Characterisation of low back pain

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CHARACTERISATION OF CHRONIC LOW BACK PAIN

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“Lately it occurs to me, what a long strange trip it’s been…..”

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Abstract

Chronic low back pain (CLBP) causes ongoing pain, disability and psychological suffering, at a huge personal and socio-economic cost. CLBP is a heterogeneous condition and its mechanisms are poorly understood. Characterisation and classification of low back pain (LBP) is controversial, there is disagreement on the characterisation and diagnosis of neuropathic low back pain (NuLBP) in relation to mechanical LBP (MLBP). Diagnostic uncertainty is coupled with poor clinical outcomes for treatment. There is therefore an urgent need to develop more effective assessment strategies to identify and better differentiate NuLBP from MLBP in order to facilitate a better understanding of underlying mechanisms and more successful treatments.

The primary aim of this study was to establish clinical profiles of CLBP, in particular, differences between MLBP and NuLBP using Questionnaire-based behavioural evaluation and sensory testing, structural neuroimaging (voxel based morphometry) and functional neuroimaging (arterial spin labelling). Significant differences were identified between CLBP patients and healthy controls and between NuLBP and MLBP patients in multiple behavioural domains measuring pain, function and psychological well-being. Significant differences were demonstrated in CLBP patients compared to controls in both tactile threshold discrimination and two-point discrimination and between NuLBP and MLBP in tactile threshold discrimination. Functional and structural neuroimaging showed significant differences between all groups in widespread brain regions involved in the evaluation of decision-

making and planning, mood and emotion, modulation of pain and representation of body schema.

This study has demonstrated the ability to characterise CLBP using a battery of behavioural, examination and functional and structural neuroimaging methodologies and has been able to differentiate between CLBP patients and controls and importantly, between NuLBP and MLBP patients. This work demonstrates the impact of CLBP across sensory-discriminative, affective-motivational and cognitive-evaluative dimensions of the pain experience and shows the increased impact and burden on those who suffer with NuLBP compared to MLBP.

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List of Abbreviations

Abbreviation	Full Name
2PD	Two-point discrimination
ACC	Anterior cingulate cortex
aMCC	Anterior mid cingulate cortex
ANOVA	Analysis of variance
ASL	Arterial spin labelling
BOLD	Blood oxygen level dependent
CBF	Cerebral blood flow
CES-D	Centre for Epidemiologic Studies Depression Scale Questionnaire
CLBP	Chronic low back pain
CRPS	Complex regional pain syndrome
DARTEL	Diffeomorphic Anatomical Registration Using Exponentiated Lie algebra
DLPFC	Dorso-lateral prefrontal cortex
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBA	Extrastriatal body area
EC	Euler characteristic
EEG	Electroencephalography
EPI	Echo planar imaging
EPQ-R	Eysenck Personality Questionnaire
FID	Free Induction Decay
FMS	Fibromyalgia syndrome
FSE	Fast Spin Echo
FWHM	Full width half maximum

GLM	General Linear Model
GM	Grey matter
GRF	Gaussian Random Field theory
H+	Hydrogen
IASP	International Association for the Study of Pain
IBS	Irritable bowel syndrome
LBP	Low back pain
M1	Primary motor cortex
MCC	Mid-cingulate cortex
MEG	Magnetoencephalography
MLBP	Mechanical low back pain
MNI	Montreal Neurological Institute
MOM	Mature organism model
MPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAA	N-acetyl aspartate
NAc	Nucleus accumbens
NeuPSIG	Neuropathic Pain Special Interest group
NMV	Net magnetization vector
NRS	Numeric rating scale
NSLBP	Non-specific low back pain
NuLBP	Neuropathic low back pain
OFC	Orbitofrontal cortex
pACC	Pregenual anterior cingulate cortex
pASL	Pulsed arterial spin labelling
pCASL	Pseudo-continuous arterial spin labelling
PET	Positron Emission Tomography
PHN	Post herpetic neuralgia

PLP	Phantom limb pain
pMCC	Posterior mid cingulate cortex
PPI	Present pain intensity scale
PTN	Trigeminal neuropathy
rACC	Rostral anterior cingulate cortex
rCBF	Regional cerebral blood flow
RF	Radio-frequency
S1	Primary sensory cortex
SCC	Subcallosal cortex
SCI	Spinal cord injury
SCL-90-R	Revised Symptom Checklist 90 Questionnaire
SF-36	RAND Medical Outcomes 36-Item Short Form Survey Instrument
SFG	Superior frontal gyrus
SFMPQ	Short Form McGill Pain Questionnaire
SNR	Signal to noise ratio
SPM	Statistical Parametric Mapping
STAI	State Trait Anxiety Inventory
TE	Time to echo
TMD	Temperomandibular disorder
TR	Repetition time
TTD	Tactile threshold discrimination
VAS	Visual analog scale
VBM	Voxel based morphometry
WM	White matter

Chapter 1 INTRODUCTION

"And yet the prevalence of back pain is perhaps matched in degree only by the lingering mystery accompanying it….." (Deyo 1998)

Low back pain (LBP) is the leading global cause of disability (Hoy, March et al. 2014) and affects nearly everyone at some point in their lives. For most people the problem is intermittent and does not drastically affect their quality of life. However, a significant minority develop chronic low back pain (CLBP), which can cause on-going pain, disability and psychological suffering, at a huge socio-economic cost.

It is estimated that approximately 5% of back pain is due to nerve root pathology and less than 1% of CLBP is due to underlying medical pathology (so called "red flags") (Waddell 2005). The remainder of CLBP is diagnosed as non-specific low back pain (NSLBP) as clinical assessment, imaging investigations and diagnostic testing and are unable to explain its underlying causes and mechanisms (Waddell 2005, Krismer and van Tulder 2007). Diagnostic uncertainty is inherently unsatisfactory. Waddell, writing in 2005, states "However semantically correct, nonspecific low back pain is not a good clinical diagnosis. It is intellectually and scientifically inadequate and fails to provide any biological basis for real understanding……, the Holy Grail of low back pain research is to find a way to sub-classify nonspecific low back pain" (Waddell 2005).

Diagnostic uncertainty is coupled with poor clinical outcomes for treatment. Most treatment studies show at best slight to moderate improvement in short

term outcomes across a wide range of conservative and non-conservative interventions which, unfortunately, are not sustained in the long term (van Tulder, Koes et al. 2006). Ultimately, improved diagnostic efficiency and more accurate differentation of mechanical and neuropathic LBP will lead to appropriately targeted treatment strategies and therefore improved outcomes .

This chapter will:

- Introduce a conceptual framework for the understanding of pain that will be used throughout this thesis

- Summarise the current epidemiology of LBP

- Review current methods for characterising and differentiating mechanical and neuropathic CLBP

- Review debates and controversies concerning the definition and characterisation of neuropathic pain

- Identify problems in assessment methods for characterising and differentiating mechanical and neuropathic CLBP methods

- Suggest new directions in assessment and differentiation methods based on an understanding of CNS mechanisms in CLBP

1.1 Models of Pain

1.1.1 The Three-Dimensional Model Of Pain

Throughout this thesis I adopt an approach that accepts that the sensory-discriminative, affective-motivational and cognitive-evaluative dimensions of pain are inherently linked (Melzack and Casey 1968, Mollet and Harrison 2006, Wiech and Tracey 2013). Although this view is no longer controversial, the emergence of models incorporating purely non-biomedical elements is a relatively recent phenomenon. In the following paragraphs I will briefly summarise the development of current models used to stratify the experience of chronic pain.

1.1.2 Biomedical Models Of Pain

The traditional Cartesian view of pain as a nociceptive, stimulus-related reflex phenomenon was prevalent throughout much of the 20thC. In this model pain was seen as a straightforward transmission of pain impulses via specific pain fibres along specific pain pathways to a pain centre in the brain (specificity theory). Pain experience was therefore considered proportionate to injury and pathology. There was little room for the psychological experience of pain in this model. Cartesian dualism saw the body as a machine and though the mind (or soul) existed it had nothing to do with the experience of pain. Pain treatment involved blocking the transmission of impulses to the pain centre in the brain by pharmacological or surgical means. Unfortunately, many patients with chronic pain did not benefit from this approach. In addition, many patients with chronic pain (and there is no

better example than back pain) did not demonstrate clearly identifiable signs of peripheral pathology. These patients, and those that failed to get better, were labelled as malingerers, either lacking in moral fibre ('workshy') or else psychologically disturbed (Waddell 2004). In the second half of the 20thC, however, researchers and clinicians increasingly challenged specificity theory.

1.1.3 Melzack And Wall: Gate Control Theory And The Three-Dimensional Model Of Pain

Melzack and Wall's gate control theory was the first to posit central nervous system mechanisms for the modulation of pain, to explain the non-linear relationship of pain stimulus to intensity (Melzack and Wall 1965). A few years later, Melzack and Casey's proposed a three-dimensional model of pain as "sensory-discriminative", "affective-motivational" and "cognitive-evaluative" that clearly outlined the role by which cognitive and psychological processes (inherently associated with brain function) are capable of modulating nociceptive stimuli (Melzack and Casey 1968). Stimulus magnitude is not enough to explain pain perception. For instance, in situations where the threat value of pain is less than a greater threat, the pain response may be attenuated (Moseley 2007). "Battle field analgesia" is a well-documented phenomenon in which the relative importance of dealing with the task in hand (ie the supreme motivational importance of survival) overrides the threat value of injury, resulting in analgesia. Conversely, in other circumstances, pain may appear out of proportion to an injury (Melzack and Wall 1996). Moreover, in many common clinical chronic pain conditions,

including CLBP, it is often difficult to identify pathology commensurate with symptoms or any pathology at all (Melzack and Wall 1996, Koes, Tulder et al. 2006). In fact, damage/nociception is not even necessary for pain perception; pain may be induced by hypnosis in the absence of any noxious stimulus (Derbyshire, Whalley et al. 2004).

1.1.4 **The 'Neuromatrix'**

Famously, phantom limb pain phenomena after amputation and spinal cord injury, inspired Melzack to the development of a new conceptual pain model (the 'neuromatrix') (Melzack 1990, **Melzack** 1999, Melzack 2001). The presence of pain in the absence of inputs from the body (but which is felt as keenly as pain that derives from peripheral injury) suggests strongly that brain neural networks underlie and subserve the experience of pain and that, although peripheral mechanisms can obviously be the cause of pain, pain is not exclusive to these peripheral mechanisms. In addition, the concept of a body identified as the 'self', distinct from the world around it, is genetically inherited and produced by the brain; it is not dependent on the periphery or spinal cord, though it may be modified by peripheral input. Melzack proposed that the anatomical substrate of the 'Body-Self Neuromatrix' consists of networks of 'neuromodules' of input areas (mediating sensory, affective and cognitive processing), which produce the outputs that together comprise the multi-dimensional nature of the pain experience. The process is cyclical; the input and output process converge in a continuing cycle of evaluation and assessment to form a characteristic dynamic 'neurosignature' composed of the activation and processing patterns of the neuromatrix, that is unique to

the individual. The qualitative experience of pain is not inherent in the properties of the injury but is generated by the unique configuration and convergence of the components of the matrix, whose unique patterns account for the non-uniform qualities of every sufferer's pain experience. An unfortunate development has been that the original neuromatrix theory has been confused by the development of a specific 'pain neuromatrix' based on the anatomical findings from imaging studies. I feel it is important that a distinction between the two is made clear and will discus the construct of a 'pain neuromatrix' later in this thesis.

1.1.5 **The Mature Organism Model (MOM)**

Melzack's neuromatrix model was reconceptualised by Gifford in terms of evolutionary biology (Gifford 2013). The mature organism model (MOM) took as its starting point that all organisms look to maintain homeostasis. In response to a homeostasis-threatening situation (which may or my not be nociceptive; it may be sensory, internally or externally generated, cognitive or affective), the individual (organism) scrutinises and evaluates the internal and external environment. Based on this evaluation, the individual decides on a course of action, involving any number of output responses (motor, sensory, autonomic, cardiovascular, immune) that may be generated to deal with the threat. Pain is one of these possible responses. The MOM emphasises the role of the organism in scrutinising the environment in order to approach a reward or withdraw from a threat, in the manner of all organisms from the most simple to the most complex.

1.1.6 **Salience**

Patients with CLBP are involved in an ongoing assessment of internal and external stimuli, in order to evaluate potential threats and rewards based on the saliency of competing stimuli. Salience is defined as “the physical distinctiveness or conspicuity of a stimulus, a relative property that depends on its relationship to the other surrounding stimuli” - stimulus saliency is dependent not only on its inherent properties, but also on its context (Legrain, Iannetti et al. 2011). Pain is usually associated with danger, as a warning of an actual, or perceived, threat to well-being and homeostasis (Melzack and Wall 1996) and is therefore inherently salient. There is compelling evidence that the saliency of a stimulus (in other words the magnitude of the threat associated with the stimulus, which may or may not in itself be noxious) is a key factor in an emergent pain response and that saliency is intimately linked to both endogenous and exogenous pain modulation (Borsook, Edwards et al. 2013). Pain sensory-discrimination and affective-motivational behavioural responses are therefore intimately connected to the meaning of the pain itself (cognitive-evaluative).

1.1.7 **Biopsychoscial Models**

The three-dimensional model of pain has been utilised in numerous ways to provide a number of alternatives to the classical biomedical Cartesian model. Most of these models can be loosely termed ‘biopsychoscial’ (Engel 1977), as they acknowledge the central role of psychological, cognitive and environmental factors in the pain experience. In addition, they serve as

conceptual frameworks around which treatment approaches can be developed. For instance, the operant conditioning model, developed by Fordyce in the 1970s focuses the modification of chronic maladaptive pain behaviours with positive and negative reinforcement (Fordyce 1976). In addition, models were developed to include cognitive as well as behavioural elements (Turk 1983). Specifically, the fear-avoidance model (Lethem, Slade et al. 1983, Slade, Troup et al. 1983, Vlaeyen and Linton 2000) and, drawing on many of its approaches for low back pain, the Glasgow back pain model (Waddell, Main et al. 1984) incorporate patient-centred (and occasionally therapist-centred!) anxieties (catastrophising) in underlying pain pathology, to describe a framework in which the pain sufferer fails to confront and overcome a threatening pain situation, instead becoming trapped in a vicious circle of pain, disability driven by fear of pain.

1.2 **Low back Pain – the Problem**

1.2.1 **Incidence**

The lifetime prevalence of low back pain is reported between 70% up to 84% of the adult population (Andersson 1999, Maniadakis and Gray 2000, Wand and O'Connell 2008, Savigny, Watson et al. 2009). Although back pain in childhood is relatively rare, by the end of adolescence 50% of the general population will have also experienced an episode (Balague, Troussier et al. 1999). Incidence rises with age, peaking between the ages of 35-55 (Burton, Balague et al. 2006). In the UK, one-third of adult population is affected each year with around 20-25% consulting their GP (Dunn and Croft 2005,

Macfarlane, Jones et al. 2006). Other studies suggest these figures may be even higher; Carey and colleagues reported that more than 20% of patients denied ever having had LBP when interviewed 4 to 16 months after an acute episode requiring a medical consultation (Carey, Garrett et al. 1995).

1.2.2 **Prognosis**

Conventionally, low back pain is categorised by its duration: acute (<6 weeks), sub-acute (6 weeks - 12 weeks) and chronic (>12 weeks) (Waddell 2004). However, this convention is arbitrary; the definition of acute and chronic is not based on any pathologic or disease process or in relation to underlying mechanisms (Apkarian, Baliki et al. 2009). Most people with acute low back pain have a favourable prognosis with pain and disability improving rapidly during the first month in the region of 58% and full recovery occurring within 3 months (Pengel, Herbert et al. 2003).

However, there is evidence that the experience of many sufferers is rather different. For those whose symptoms resolve, more than 28% of cases recur within 6 months (Cassidy, Cote et al. 2005) and 73% of patients have at least one recurrence within 12 months. Recurrences may occur more frequently and be more severe depending on the length and severity of previous episodes (Von Korff, Balderson et al. 2005). For those whose symptoms do not resolve fully, after three months little further improvement is observed for pain, disability, and return to work (Pengel, Herbert et al. 2003). One year after a first episode of back pain between 60-80% of people still have pain and disability (Croft, Macfarlane et al. 1998, Hestbaek, Leboeuf-Yde et al.

2003) and 16% of those initially unable to work are still not working after one year (Hestbaek, Leboeuf-Yde et al. 2003). Overall, less than one third of cases resolve annually and more than 40% of those with low back pain have persistent symptoms (Pengel, Herbert et al. 2003, Cassidy, Cote et al. 2005). Therefore, it has been suggested that the acute/sub-acute/chronic classification system is arbitrary and rigid and not applicable to a large proportion of the back pain population (Croft, Dunn et al. 2006, van Tulder, Becker et al. 2006).

1.2.3 **Costs**

Low back pain is associated with substantial socioeconomic costs. Back pain typically affects the working population, as incidence peaks between 35 and 55 years of age (Andersson 1999). In 2005, the Trades Union Congress (TUC) estimated that 4.9 million working days per year were lost due to back pain (T.U.C 2005). Direct health care costs in the UK in 1998 were £1632 million, including £565 million spent on non-NHS health care costs. If indirect costs due to work absenteeism and disablement are added to the direct costs then the true cost of LBP is substantially higher. In 2006, the total costs of back pain in the Netherlands in 1991 were more than 4 billion Euro, in the United Kingdom in 1992 more than 2.7 billion Euro, and in Sweden in 1995 more than 2 billion Euro (van Tulder, Becker et al. 2006). It is estimated that 80% of the total costs for the management of back pain in the UK are used on the 10% of people who develop chronic LBP (NICE clinical guideline 88 from www.nice.org.uk/CG88.)(Nachemson 2000)

The figures above describe a massive economic problem. The rates of chronicity in the previous section highlight that for many people, low back pain refuses to go away, at a huge personal cost not only economically but also in terms of family and social relationships and general mental health (Croft, Papageorgiou et al. 1995, Hoogendoorn, van Poppel et al. 2000, Currie and Wang 2004, Linton 2005, Linton 2011). The primary motivation for this study is to better understand and characterise CLBP in order to target treatments to relieve the suffering associated with this often-debilitating condition.

1.3 Classification of LBP

1.3.1 Diagnostic Low Back Pain Triage

Specific guidelines for diagnostic triage vary internationally but all recommend grouping patients with LBP into three categories (Deyo, Rainville et al. 1992, Waddell 2004, Airaksinen, Brox et al. 2006, Rubinstein and van Tulder 2008, Koes, van Tulder et al. 2010, Lee, Gupta et al. 2013):

1. Suspected or confirmed serious pathology, which may also include inflammatory pathology (so called “red flags”)

2. Mechanical low back pain (also known as ‘Ordinary’ or ‘simple’ back pain or non-specific low back pain

3. Nerve root pain

1.3.2 **Mechanical Low Back Pain**

MLBP is described as pain, tension, soreness and/or stiffness in the lower back region (defined as the area bounded by the bottom of the rib cage and the buttock creases. Dysfunction or pathology in any one of numerous structures in the back (for instance, intervertebral disc degeneration or herniation, facet joint degeneration, spondylolisthesis, sacro-iliac joint degeneration) is thought to contribute to signs and symptoms of back or leg pain (Nachemson 2000, Bogduk 2010). Mechanical pain is caused by activation of nociceptors in peripheral tissues and viscera by noxious stimuli and is therefore also known as nociceptive pain. Nociceptive transmission is relayed to second order neurons in the spinal cord and thence to supra-spinal centres. The noxious input generates a complex output response, modulated by supra-spinal cognitive and affective processing, involving motor, hormonal, cardiovascular and autonomic responses. Tissue damage also initiates an inflammatory response leading to a change in local metabolism and cellular activity. This process, known as peripheral sensitisation, leads to local and distal hypersensitivity (hyperalgesia and allodynia) (Costigan and Woolf 2000). Furthermore, it is important to note that alterations in afferent sensory inputs result in sensitisation of the spinal cord and supraspinal sites. It is essential therefore that we understand that the presence of hypersensitivity is not, in itself, evidence of peripheral nerve involvement.

1.3.3 **Non-Specific MLBP**

It is not possible to find a specific cause for the pain in the majority of MLBP sufferers. More than 80% of patients with MLBP are therefore said to suffer from non-specific low back pain (NSLBP). NSLBP is essentially a diagnosis arrived at by exclusion of red flags, systemic inflammatory disorders or nerve root pain (Koes, Tulder et al. 2006). Therefore, by default, NSLBP is described as mechanical low back pain (MLBP) in that pain is assumed to originate from somatic nociceptive structures of the lower back.

1.3.4 **Low Back Pain With Leg Pain: Categorisation In To Somatic And Radicular Components**

Patients with low back pain frequently report the presence of distal symptoms radiating into the buttocks and lower limbs. Radiating back pain is usually divided into neuropathic radicular (leg pain resulting from sensory nerve root or dorsal root ganglia irritation or compression) or somatic pseudoradicular (leg pain arising from non-nervous tissue, therefore by definition mechanical/somatic) (Saal 2002). Patients with mechanical somatic leg pain are generally described as complaining of axial back pain that is worse than leg pain, with leg pain generally not radiating past the knee and with no neurological signs on examination (Waddell 2004).

1.3.5 **Neuropathic Radicular Low Back Pain**

Back pain patients with neuropathic nerve root pain are described as having leg pain that is worse than back pain, which radiates below the knee to the

foot or toes. They may have all, or a combination of the following; pain and/or parasthesia in a dermatomal distribution (most commonly L5, S1), weakness and reduction or loss of tendon reflexes - all in the distribution of a nerve root (Waddell 2004, Konstantinou and Dunn 2008).

Estimation of the prevalence of lumbosacral nerve root pain in the general population varies from as little as 1.2% to as much as 66%. (Freynhagen, Baron et al. 2006, Freynhagen, Baron et al. 2006, Hill, Dunn et al. 2008, Konstantinou and Dunn 2008, Beith, Kemp et al. 2011). The most likely reason for the large variability is confusion over what constitutes radicular leg pain and the frequent use of the term ‘sciatica’ in both clinical and research settings. Sciatica is most commonly used to describe the presence of lumbosacral nerve-root related leg pain. Unfortunately, sciatica is often applied as a catch-all term for back pain with leg pain symptoms. However, as discussed in section 1.3.2, leg pain in itself is not definitive evidence of a neuropathic component – leg pain may arise as referred pain from somatic structures in the back. In addition, there is little consistency in diagnostic methodology to arrive at a diagnosis of radicular nerve root related low back pain, both clinically and in research settings. Prevalence rates therefore likely reflect the confusion in clinical and research settings regarding the diagnosis of mechanical and neuropathic leg pain (Waddell 2004, Konstantinou and Dunn 2008). In sections1.4, 1.5 and 1.6 below I will discuss the challenges, controversies and debates regarding the assessment, diagnosis and definition of mechanical and neuropathic low back pain. In particular, I will

highlight methodological and diagnostic controversies and debates regarding the definition of neuropathic pain itself.

1.4 Methods of Assessment

1.4.1 Radiographic And Imaging Investigations For MLBP

There is an abundance of radiographic and MRI imaging studies that show a non-linear association between structural abnormalities, degeneration, signs of injury, pathology and pain (Jarvik and Deyo 2002, van Tulder, Becker et al. 2006). Up to 47% of patients with LBP have been shown to have normal magnetic resonance imaging (MRI) of the lumbar spine (Savage, Whitehouse et al. 1997). Conversely, asymptomatic individuals also show a high prevalence (20–76%) of lumbar disc abnormalities with MRI (Jensen, Brant-Zawadzki et al. 1994, Boos, Semmer et al. 2000). Similarly, other studies also demonstrate that radiographic evidence of osteoarthritis in other bodily locations does not correlate well to reports of pain or function (Teichtahl, Wluka et al. 2008). There is also little correlation between the degree of structural abnormality and treatment outcomes (Kleinstuck, Dvorak et al. 2006). Identification of disc abnormalities in asymptomatic subjects also does not predict future episodes of back pain or sciatica. MRI cannot be used as a screening tool to identify risk of developing LBP (Savage, Whitehouse et al. 1997).

Nevertheless, investigations are still routinely ordered, in spite of evidence that the use of radiography or MRI for NSLBP does not aid diagnosis, result

in better treatment outcomes (Kendrick, Fielding et al. 2001) or offer reassurance for patients worried about their back pain (van Ravesteijn, van Dijk et al. 2012). 5% of all x-rays in the NHS are of the lumbar spine (Kendrick, Fielding et al. 2001).It is estimated that as many as 50% of investigations are most likely unnecessary (Halpin, Yeoman et al. 1991).

1.4.2 Radiographic And Imaging Investigations For Lumbar Radicular Pain

Guidelines recommend MRI for lumbar nerve root patients with chronic non-resolving symptoms seeking medical intervention (van Tulder, Becker et al. 2006). However, as with non-specific MLBP, there is also an uncertain correlation between imaging signs and patient symptoms. Patients frequently present with neuropathic symptoms without any objective imaging signs; in a recent study, only 28% of LBP patients identified with neuropathic pain components using the painDETECT screening questionnaire had MRI scans identifying nerve root impingement (Beith, Kemp et al. 2011). Conversely, the majority of lesions to the nervous system do not result in neuropathic pain nor correlate to symptoms (Bennett 2003). In the lumbar spine, the presence of disc prolapse or nerve root compression does not necessarily result in neuropathic symptoms (Boden, Davis et al. 1990). Neither positive or negative lumbar investigation findings are able to confirm or deny a diagnosis of both mechanical and neuropathic LBP.

1.4.3 **Clinical Examination: MLBP**

Evidence for the accuracy and diagnostic benefit of clinical examination procedures and interventional diagnostic testing for LBP is also limited (Carragee, Paragioudakis et al. 2000, Huston and Slipman 2002, Saal 2002, Airaksinen, Brox et al. 2006). A recent systematic review found low reliability of most commonly used examination procedures, including tests for evaluation of muscle tension or spasm, spinal instability, and provocative manoeuvres for diagnosing SI joint pain or facet joint pain (Rubinstein and van Tulder 2008).

Of all common examination tests, only manual pain provocation tests have any inter-tester reliability (Rubinstein and van Tulder 2008). CLBP patients frequently present with widespread pain and tenderness. Studies show that patients with CLBP exhibit greater tenderness and lower mechanical pain thresholds compared to healthy controls not only over the lumbar spine but also elsewhere (R Jason S Giesbrecht). CLBP patients also report more pain to noxious thermal stimulation (Kleinbohl, Holzl et al. 1999) and to saline injection at distal sites (O'Neill, Manniche et al. 2007). However, widespread pain and greater sensitivity is suggestive of central sensitization mechanisms rather than underlying pathology; studies have been unable to find any relation between tender points and underlying pathology nor abnormalities in the tender points themselves (Kendrick, Fielding et al. 2001).

1.4.4 **Clinical Examination Of Lumbar Radicular Pain**

Passive straight leg raising (SLR) is the most commonly used clinical test used to diagnose lumbar radicular pain and to differentiate neuropathic nerve root pain from MLBP. Numerous reviews have studied its sensitivity and specificity. The consensus of these studies is that the test is highly sensitive but is not very specific and is not, therefore, a useful tool to differentiate neuropathic from mechanical pain, nor to confirm or deny its presence (Deyo, Rainville et al. 1992, van den Hoogen, Koes et al. 1995, Vroomen, de Krom et al. 1999, Rubinstein and van Tulder 2008). Furthermore, pain that is due to hamstring tightness may lead to false positives (Airaksinen, Brox et al. 2006, Scaia, Baxter et al. 2012).

Recent reviews have found poor diagnostic performance of most common physical tests (such as passive straight leg raising, reflex examination and neurological examination of muscle weakness and sensory loss) to identify lumbar radiculopathy due to disc herniation and to differentiate neuropathic nerve root pain from MLBP (Van der Windt D.A.W.M. 2010, Al Nezari, Schneiders et al. 2013, Iversen, Solberg et al. 2013). Evidence for the diagnostic utility of nerve root blocks is also limited (Datta, Manchikanti et al. 2013). Physical examination also shows limited agreement with the results of electro diagnostic nerve testing. Positive and negative neurological examination findings correlate poorly with electroneuromyographic testing (Inal, Eser et al. 2013).

1.5 Are We Failing To Detect Significant Neuropathic Elements In Patients With LBP?

The previous sections have highlighted the difficulties in identifying patients with radicular nerve root pain with standard examination procedures. The clinical presentation of patients with signs and symptoms of possible neuropathic back pain is often different from what is described in clinical textbooks. Many patients with symptoms of radicular nerve root pain do not demonstrate signs of nerve root compression on MRI and may also fail to demonstrate positive examination findings. Equally, many patients with positive examination findings do not show classical patterns of pain distribution, with attendant neurological changes. Failure to demonstrate consistency in signs and symptoms of neuropathy inevitably leads to a rejection of a neuropathic diagnosis. However, recent work indicates that current clinical examination methods and characterisation paradigms may fail to detect neuropathic components in many patients with LBP with both axial and distal presentations. The issues raised from this body of work are central to debates on the definition, diagnosis and categorisation of neuropathic pain that have taken place between members of the International Association for the Study of Pain (IASP) over the last 15 years. This debate is central to the issues of characterisation and diagnosis of neuropathic pain outlined in this thesis.

1.6 **Definitions Of Neuropathic Pain: A Mechanisms Or Disease Based Approach?**

The current International Association for the Study of Pain (IASP) definition of neuropathic pain, updated in 2011, is “Pain caused by a lesion or disease of the somatosensory nervous system” (https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698) (see Appendix 1 for full definition). This definition replaces the previous definition from 1994 of “pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system”.

The taxonomy of neuropathic pain has inspired substantial debate over the last decade. In 2008, an IASP Neuropathic Pain Special Interest Group (NeuPSIG) was convened in order to arrive at a clear definition of neuropathic pain and how best to distinguish it from nociceptive pain. A resulting paper appeared in the journal Neurology (Treede, Jensen et al. 2008) with a definition more or less identical to the current IASP definition. The key difference between the 1994 and later definitions centred on the term ‘dysfunction’, which was dropped from the earlier definition and replaced by ‘disease’. Disease, in the IASP statement is defined as the underlying cause of the identified lesion to the nervous system (i.e. stroke). The dropping of the term dysfunction clearly fixes the categorization of neuropathic pain as requiring evidence of a lesion or disease state, as ‘objective’ markers of pathology that give a degree of confidence to a neuropathic diagnosis. Too many conditions, it was felt, whose mechanisms

were essentially unknown (i.e. fibromyalgia, CRPS) were falling under the "umbrella of neuropathic pain" (Jensen, Baron et al. 2011). Without a link to an identifiable lesion, the relationship of "structure to function" could not be determined and consequently, the stringency of a neuropathic diagnosis was weakened. A diagnosis of neuropathic pain without a lesion or disease state risked becoming vague and insignificant, an umbrella term for conditions in which the mechanisms were unusual and unclear. Additionally, it was argued that giving a (false) neuropathic diagnostic label to conditions without any clear lesion or disease state might prevent clinicians and researchers from further exploration of underlying mechanisms (Jensen, Baron et al. 2011). A grading system of certainty of neuropathic pain diagnosis was proposed ('definite', 'probable' or 'unconfirmed') based on positive history, somatosensory abnormality on clinical examination and a confirmatory diagnostic test. By these criteria, to arrive at a 'definite' diagnosis of neuropathic radicular leg pain, a) the history would have to indicate leg pain worse than back pain in a dermatomal distribution, b) examination should demonstrate positive altered sensation in the dermatome and c) MRI would show the presence of nerve root compression. However, possible negative implications and consequences of not achieving 'definite status' in a three-tiered system were highlighted (Eisenberg 2011). A patient with 'probable' symptoms might be considered somehow 'less' neuropathic than a patient with a 'definite' diagnosis. It was also suggested that failure to meet the grading criteria might result in patients having their symptoms questioned and/or result in treatment being withheld, either by clinicians or by insurance companies. For instance, the radicular patient mentioned above might

present with a positive symptom history but with a negative MRI and pain outside the suggested innervation territory of the injured dermatome. The clinical experience of this author is that many, if not the majority of CLBP patients with severe back and leg pain would fail to meet all three criteria. In fact, many of these patients end up in pain management clinics *precisely because they fail to fit into neat diagnostic criteria* and conform to standard neurological textbook descriptions. These concerns were raised in a reply to the authors of the revised definition (Lynch, Clark et al. 2011) that animal studies demonstrate spread of sensory abnormalities outside the territories of lesioned nerves (Tal and Bennett 1994, Malan, Ossipov et al. 2000) which corresponds to the clinical experience of patients with nerve lesions (Koltzenburg 2005).

Alternative diagnostic paradigms have been suggested that accommodate the heterogeneity of clinical presentations of patients with signs and symptoms of neuropathic pain. Instead of requiring a lesion or disease state, neuropathic diagnosis requires a sensitive profiling based around pain descriptions and symptom clusters as well as sensory profiling by clinical examination (Attal, Bouhassira et al. 2011, Bouhassira and Attal 2011, Baron, Forster et al. 2012). Underlying this approach is the belief that neuropathic pain, rather than being a single entity common across all disease states, is instead characterised by specific mechanisms that may be identified by different constellations of symptom clusters. A clinical condition identified by a homogenous label such as ‘low back pain’ may in fact encompass different symptom clusters and sensory examination profiles that

suggest different underlying mechanisms for each presentation, rather than one homogenous neuropathic pain mechanism.

Screening tools have been developed to recognize symptom clusters suggestive of neuropathic pain and are widely used both in clinical and research settings as an important aid in diagnosis (Bennett, Attal et al. 2007, Jones and Backonja 2013). These screening tools are generally designed to alert the clinician or researcher to the presence of a possible neuropathic component – the diagnosis is then confirmed by physical examination (and in current IASP taxonomy by the presence of a confirmatory lesion and disease state). No sign or symptom, in itself, is pathognomonic of neuropathic pain (Rasmussen, Sindrup et al. 2004, Bennett, Attal et al. 2007, Dworkin, Jensen et al. 2007, Jones and Backonja 2013). Although signs and symptoms may indicate underlying mechanisms, signs and symptoms are not equivalent with mechanisms (Finnerup and Jensen 2006). In fact the current IASP definition of neuropathic pain explicitly states, “The presence of symptoms or signs (e.g., touch-evoked pain) alone does not justify the use of the term neuropathic”. Nevertheless, several large-scale studies have shown heterogeneity of symptom and sensory profiles in patients with the same clinical condition (Attal, Fermanian et al. 2008). Baron and colleagues (Baron, Forster et al. 2012) identified five different profiles from two studies combining 4200 patients with post herpetic neuralgia, painful diabetic polyneuropathy and painful radiculopathy using the painDETECT questionnaire (Baron, Tolle et al. 2009, Mahn, Hullemann et al. 2011). Clusters of different neuropathic sensory profiles in CLBP have also recently

been demonstrated using the DN4 questionnaire in a mixed LBP cohort (Attal, Perrot et al. 2011) and in axial LBP patients using the painDETECT questionnaire (Forster, Mahn et al. 2013). Importantly, in the context of this study, these LBP studies demonstrate that neuropathic pain is not restricted to patients that present with a typical radicular presentation. Freynhagen and colleagues provided further evidence of possible neuropathic components in patients with a diagnosis of non-neuropathic low back pain (Freynhagen, Rolke et al. 2008). Subtle subclinical sensory deficits were found in the distal dermatomes of the foot in a group of fifteen patients with chronic so-called ‘‘pseudoradicular’’ low-back pain radiating into the leg, as well as in in a radicular (neuropathic) group of twelve patients, using somatosensory profiling. Radicular patients had more pronounced (but not statistically significant) sensory deficits. In the radicular group, the sensory deficit and the pain distribution were present in the same dermatomal area; both areas were congruent. In the pseudoradicular group, however, the pain radiation and the sensory deficit were not congruent; in these patients pain was not felt in the foot. Contralateral sensory deficits were also found in both groups of patients The authors proposed that the subclinical sensory deficits identified in the pseudoradicular low-back pain patients are evidence of an occult neuropathic component in a group whose symptoms have been previously been associated exclusively with somatic mechanical pain. Furthermore, the authors suggested that in addition to low back pain classification categories of nociceptive and neuropathic, another category, described as ‘mixed’ or ‘unclear,’ be included.

This study employs the painDETECT screening tool developed by Freynhagen and colleagues (Freynhagen, Baron et al. 2006) to initially characterise our CLBP cohort into patients with a significant likelihood of either mechanical pain or neuropathic pain. The painDETECT questionnaire was specifically developed in order to identify neuropathic components in LBP and, in particular, to discriminate between low back pain of mechanical and neuropathic origin. PainDETECT has been shown to have a high sensitivity (85%), specificity, (80%) and positive predictive accuracy (83%) in LBP (Freynhagen, Baron et al. 2006). However, its usefulness in other conditions has been questioned (Tampin, Slater et al. 2013, Elias, Yilmaz et al. 2014). Throughout this study I have decided to call patients identified by painDETECT as having a significant neuropathic component to their pain, neuropathic low back pain patients (NuLBP). It is important to note that this does not imply that they are patients with a clearly identifiable nerve root lesion, according to conventional diagnostic triaging paradigms. Rather these are patients, who demonstrate *a significant neuropathic component* to their pain irrespective of their lesion or pathological status.

Although the painDETECT questionnaire has been designed as a screening tool and screening tools consistently fail to identify 10-20% of patients diagnosed with neuropathic pain by expert clinicians (Bennett, Attal et al. 2007), the decision was made to use the questionnaire to characterise our LBP groups without the use of a confirmatory diagnosis from a specialist clinician. The principal reason for this decision was that we sought to classify subjects with a significant neuropathic component to their pain as NuLBP

patients, rather than patients with specific nerve root or stenotic presentations that correspond to with conventional LBP triaging protocols. It is a primary hypothesis of this thesis that there are a significant number of people with LBP with a significant neuropathic component that is inconsistently identified who subsequently fail to receive appropriate treatment. The painDETECT questionnaire is specifically designed to identify this cohort of patients, who present with an occult neuropathic component that may not be identified by examining clinicians.

Furthermore, in a research context, use of the painDETECT questionnaire has the value of standardizing the identification of patient groups. While acknowledging the limitations of the painDETECT questionnaire, use of the questionnaire allows a consistent approach to all patients and allows comparison across studies by the use of an objective measure. Clinical assessment is also a qualitative rather than quantitative tool and therefore subject to variability. Clinical tests also have limitations with sensitivity, specificity as detailed in section 1.4.4. I feel that identification of groups by screening questionnaires reduces therefore reduces possible inconsistencies in patient selection criteria.

1.6.1 What Are The Mechanisms That Underlie Changes In Sensory Profiles In Patients With No Identifiable Signs Of A Lesion Or Disease State?

Several explanations have been offered for ‘mixed’ or ‘unclear’ presentations of symptoms in CLBP. For instance, an acutely injured or degenerative

lumbar disc might leak inflammatory mediators (such as substance P), chemically activating local nociceptors, while at the same time irritating nerve root fibres in the same or neighbouring spinal segment (Coppes, Marani et al. 1997). The chemical irritation would result in neuropathic pain, independent of mechanical compression of the nerve root and subsequent overt neurological sensory or motor deficits. Widely diffused inflammatory mediators from a damaged disc may also explain the contralateral sensory deficits found in both radicular and pseudoradicular patients (Freynhagen, Rolke et al. 2008). In addition, a transition from pseudoradicular to radicular pain could result from a gradual increase of nerve compression from a herniated disc affecting, in order, myelinated A beta nerve fibres, A delta cold fibres, A delta nociceptive and finally C fibres. A similar pattern of fibre damage has been reported in animal studies by several authors (Nygaard, Kloster et al. 1998, Yamashita, Kanaya et al. 2002).

However, mechanisms other than peripheral neuropathy may explain unorthodox clinical presentations. Pain and sensory deficits are associated with supraspinal plasticity in numerous clinical pain conditions such as patients with complex regional pain syndrome (CRPS) (Flor 1995, Juottonen, Gockel et al. 2002, Maihofner, Handwerker et al. 2003, Pleger, Tegenthoff et al. 2004, Maihofner, Forster et al. 2005) and phantom limb pain (PLP) (Flor, Elbert et al. 1995, Lotze, Flor et al. 2001). Alterations in QST profiles may not therefore be related to peripheral events but instead to spinal/supraspinal plasticity in the central nervous system. However, unlike disease-based lesions, these changes are not observable with conventional examination

methodologies. In this thesis I intend to use novel methods of sensory clinical profiling and structural and functional neuroimaging to explore the relationships between sensory and neuroimaging profiles and investigate whether these can be utilised to identify differences between CLBP patients and healthy controls and also between LBP patients with mechanical and neuropathic presentations.

1.7 **Supraspinal Plasticity**

In addition to LBP, there is increasing evidence that patients suffering from conditions assumed to be entirely somatic in origin (i.e hip and knee osteoarthritis (Kosek and Ordeberg 2000), patello-femoral (Jensen, Kvale et al. 2008) and shoulder pain (Gwilym, Oag et al. 2011) as well as other pain conditions of uncertain aetiology (ie complex regional pain syndrome, phantom limb pain, fibromyalgia syndrome (Flor, Denke et al. 2001, Maihofner, Herzner et al. 2006, Moseley, Zalucki et al. 2008, Lee, Nassikas et al. 2011, Staud 2011)) present with symptoms and subtle sensory profiles that suggest a neuropathic component. However, these patients do not demonstrate any objective signs of a lesion to the peripheral or central nervous system. The last decade has seen a large amount of studies that have used neuroimaging techniques to explore structural, functional and chemical plasticity in the brain in response to both experimentally induced and clinical pain states (May 2007, Tracey and Mantyh 2007, May 2008, Apkarian, Baliki et al. 2009, Davis 2011, Davis and Moayedi 2013). These studies have shown objective signs of CNS plasticity and modulation in these patients, which indicate perpetuating neural mechanisms, in addition to

possible peripheral mechanisms for the maintenance of on-going pain conditions.

Neuroplasticity is defined as adaptive change in structure, function and chemistry within the nervous system (Pascual-Leone, Amedi et al. 2005) involving multiple levels from brain networks to cellular and synaptic reorganisation (Shaw 2001). Although it is commonly discussed in terms of brain plasticity, plasticity may of course occur anywhere in the nervous system (Woolf and Salter 2000) . In fact, changes that occur in the periphery are likely to be reflected in the central nervous system and vice versa. These paradigms will be tested in this thesis. I aim to show evidence of both structural and functional central nervous system changes associated with low back pain. Chemical plasticity is beyond the scope of this thesis and will only be discussed where the findings from other groups support/negate, extend or inform the discussions presented. I will be making reference to the body of work on brain-related changes in chronic pain that initially influenced this thesis in chapters 4 and 5. This thesis therefore aims to characterise the behavioural and examination correlates of CLBP (differentiating mechanical and neuropathic phenotypes) together with the functional and structural brain changes associated with the physical and emotional demands of living with on-going pain.

1.8 Why Is It Important To Accurately Identify Patients With Neuropathic Pain?

A failure to identify patients with occult neuropathic symptoms is of more than mere academic interest. Neuropathic pain patients report significantly higher pain and disability scores, reduced quality of life and higher psychological co-morbidities compared to non-neuropathic pain patients (Freynhagen, Baron et al. 2006, Jensen, Chodroff et al. 2007, Smith, Torrance et al. 2007, Smith and Torrance 2012). Recent data suggest there may be a failure to identify many chronic back pain patients with a significant neuropathic component. Freynhagen's and colleagues found that 37% of patients with CLBP attending pain management clinics in Germany had a significant neuropathic component to their pain (Freynhagen, Baron et al. 2006). Mayne and Thacker in 2007 (personal communication), also using the PainDETECT questionnaire, found a significant neuropathic pain component in 22% (n=201) of patients with low back pain referred to physiotherapy at a major London NHS Foundation Trust. These figures are clearly higher than standard estimates for the prevalence of neuropathic pain in LBP (Waddell 2005), which estimate that only 5% of patients presenting with LBP are likely to have neuropathic pain.

Diagnostic uncertainty is coupled with poor clinical outcomes for treatment. Most treatment studies show at best slight to moderate improvement in short term outcomes across a wide range of conservative and non-conservative interventions which, unfortunately, are not sustained in the long term (van

Tulder, Koes et al. 2006). A prolonged painful response is characteristic of neuropathic pain long after an initiating stimulus has passed and tissue healing has occurred (Woolf and Salter 2000). A failure to identify patients with occult neuropathic symptoms may lead to inappropriate targeted treatments directed towards somatic tissue, resulting in unnecessary ongoing pain, disability and suffering. There is therefore an urgent need to develop more effective assessment strategies to identify and better differentiate neuropathic from mechanical low back pain. Ultimately, improved diagnostic efficiency and more accurate differentation of mechanical and neuropathic LBP will lead to appropriately targeted treatment strategies and therefore improved outcomes.

1.9 **Overall hypotheses of the study**

1.9.1 **Hypothesis one:**

There are differences between CLBP and controls across a range of domains:

1. Questionnaire-based behavioural characterisation
2. Sensory examination profiling
3. Functional neuroimaging (ASL)
4. Structural neuroimaging (VBM)

1.9.2 **Hypothesis two:**

There are differences between MLBP and NuLBP across a range of domains:

1. Questionnaire-based behavioural characterisation

2. Sensory examination profiling

3. Functional neuroimaging (ASL)

4. Structural neuroimaging (VBM)

1.10 **Aims of the study**

The primary aim of this study is to better characterise and clinically profile patients with CLBP. In particular, I wish to characterise differences between MLBP and NuLBP using using a battery of methodologies: Questionnaire-based behavioural evaluation and sensory testing, structural neuroimaging (voxel based morphometry) and functional neuroimaging (arterial spin labelling). I hope to establish that these modalities have the ability to differentiate not only between CLBP patients and controls but importantly, between patients with mechanical and neuropathic chronic back pain.

It is hoped that improved differentiation will ultimately lead to better understanding of underlying mechanisms and novel and more successful treatments.

1.11 **Description Of Study Chapters.**

Following initial screening with painDETECT, the study will use novel characterisation strategies across a number of different methods to explore group differences:

- Methodology (Chapter 2). This chapter outlines the overall study design, the specific imaging methodology and the statistical analysis methods used in chapters 4 and 5.

- Questionnaire-based behavioural evaluation and sensory testing (chapter 3). This chapter uses questionnaire-based psychometric testing and sensory examination using two-point and tactile threshold discrimination to examine the clinical and behavioural profiles of CLBP.

- Structural neuroimaging (voxel based morphometry) (chapter 4). This chapter uses voxel-based morphometry to analyse structural differences in grey matter between mechanical and neuropathic back pain groups and between back pain groups and controls.

- Functional neuroimaging (arterial spin) (chapter 5). This chapter uses arterial spin labelling to analyse differences in regional cerebral blood

flow between mechanical and neuropathic back pain groups and between back pain groups and controls.

- Discussion (Chapter 6). This chapter summarises key findings in the context of the assessment and treatment of CLBP.

Chapter 2 METHODS

Preface: This chapter includes descriptions of the overall study design and an introduction to MRI Acquisition and MRI Statistical Analysis. Details are included here in order to avoid unnecessary repetition of common methodologies in chapters 4 and 5.

2.1 Study Design

2.1.1 Participants

50 LBP patients and 20 healthy controls were recruited for all three components of the study (characterisation, structural and functional neuroimaging). Patients were recruited from the Musculoskeletal Assessment Service and Physiotherapy department of Guy's and St Thomas' NHS Foundation Trust. Control subjects were recruited from colleagues at Guy's and St Thomas' NHS Foundation Trust and King's College. Subjects undergoing assessment at the hospital were asked if they would be interested in taking part in the study. If so, they were given the opportunity to ask questions and provided with an information sheet giving full details of the study. They were asked if they would agree to be contacted again by telephone or if they preferred, when they next visited the hospital to find out whether they were interested in the study and given the opportunity to ask any further questions. The same process was adhered to for colleagues recruited as controls. All subjects gave written informed consent on the day of scanning.

2.1.2 **Ethical Approval**

Formal ethical approval for the study was granted by NRES (08/H0810/51).

2.1.3 **Inclusion Criteria**

All patients had LBP for at least 12 months. Patients rated their pain on an 11 point numerical rating scale (NRS) at screening and on the day of scanning (anchors: 0=”no pain”, 10 “worst pain” imaginable”); all patients who scored 3 or greater were eligible for inclusion. All subjects were right handed. Initially, all patients who met the inclusion and screening criteria were included in the study regardless of mechanical or neuropathic status, as determined by the PainDETECT questionnaire. Although all patients were selected at random, towards the end of recruitment process it was observed that rather more MLBP than NuLBP patients had been recruited. It was therefore deemed necessary to preferentially bias selection of LBP subjects with symptoms that appeared, in the opinion of the clinician examining the patient, to suggest a significant neuropathic component, in order to balance patient numbers between the LBP groups.

2.1.4 **Screening**

Subjects were screened to meet safety criteria for 3T MRI scanning. Due to the stringent requirements of the 3T safety screening criteria, a number of subjects with a history of spinal, abdominal or soft tissue surgery, whom we were unable to provide medical notes for, were excluded from the study. Subjects were excluded if they complained of chronic or current pain

conditions other than LBP or if they were currently experiencing, or had any history of, clinically significant or unstable medical or psychological conditions that would compromise participation in the study. Altogether, 143 CLBP subjects were approached to take part in the study. Of these, 73 were unable to take part due to previous or current medical history. There were no exclusion criteria for pain medication and all subjects continued with their usual medication use. A list of CLBP subjects is listed in the appendix giving details of medication use. Medications were grouped into the following categories: Paracetamol; Paracetamol combined with opiates (ie co-codamol, co-dydramol); Opiates (ie dihydrocoedine); Non-steroidal anti-inflamatories (ie ibuprofen, diclofenac, voltarol); Anti-convulsants (ie pregablin, gabapentin) and Anti-depressants (ie amitriptyline). As differences in medication usage might significantly affect brain morphometry and perfusion, Chi-square tests were used to identify differences between the groups in medication use. Using chi-squared tests for independence (with Yate's continuity correction) no significantly different levels of medication usage were found between groups: NSAIDS X^2 = 4.06, p = .09; paracetamol X^2 = .031, p = 1.00; paracetamol and opiates combined X^2 = .675, p = .624; opiates X^2 = 4.71, p = .099; anti-convulsants X^2 = 2.279, p = .299; anti-depressants X^2 = .273, p = .909; A list of CLBP subjects is listed in Appendix 3, giving details of age, gender, diagnosis, medication use and any previous non-conservative intervention.

Prior to scanning, all subjects underwent an initial familiarisation 'scanning' session in a 'mock' scanner environment, in order to minimize participant

anxiety and to familiarise participants with the requirements of an imaging environment.

2.1.5 **Study Participation**

50 LBP patients and 20 healthy controls were recruited for all three components of the study (characterisation, structural and functional neuroimaging).

All subjects completed the questionnaire data. Due to administrative errors sensory testing data was not completed by three of the fifty LBP patients and two of the twenty controls (CLBP n = 47 (MLBP n = 24, NuLBP = 23), controls n= 18).

In the structural neuroimaging VBM study, one CLBP subject and one healthy control were excluded as inadequate structural images were obtained (CLBP n = 49 (MLBP n = 26, NuLBP = 23), controls n= 19).

In the functional neuroimaging ASL study, four CLBP subjects were excluded as inadequate functional images were obtained (CLBP n = 46 (MLBP n = 24, NuLBP = 22), controls n= 20).

2.2 Imaging the Brain: Magnetic Resonance Imaging

2.2.1 The Hydrogen Nucleus

MRI technology utilises the electromagnetic properties of hydrogen (H+) atoms in order to produce highly detailed images of the body's tissues. The nucleus of an atom is composed of two particles – protons, which have a +ve charge and neutrons, which are neutral. Orbiting the nucleus are electrons, which have a negative charge. All the particles are in motion and spin about their axes. The rotation of each particle around its axis is termed its 'angular momentum or 'spin'' and each charged particle produces a magnetic field at right angles to the direction of motion. This is termed its 'magnetic dipole moment' (MDM). H+ nuclei protons are used due to their abundance in the human body and their large magnetic moment (McRobbie, Moore et al. 2007, Huettel 2008, Westbrook 2011).

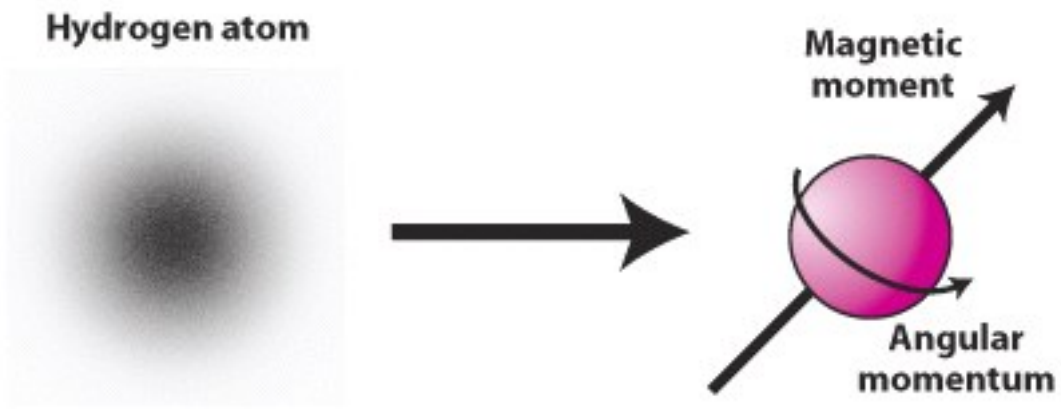

Figure 1: Magnetic Moment and Angular Momentum of a Hydrogen Atom

(from http://www.rise.duke.edu/apep/pages/page.html?001009).

2.2.1.1 **The Hydrogen Nucleus In The Magnetic Field**

An MRI scanner contains a large superconducting magnet formed of coils of wire containing electric current. The wires are kept at 269 degrees Celsius below zero in liquid helium (surrounded by a thermos-type flask) to enable resistance in the wire to drop to zero.

Before entering the magnetic field of the scanner, H+ protons are arranged in a random fashion, according to each proton's magnetic properties. Net magnetization is practically zero. When a subject enters the magnetic field, protons within the individual become subject to the external field's magnetic properties. Protons either align with the magnetic field (in classical mechanics, parallel, or in quantum mechanics, low energy state) or against it (anti-parallel or high energy state. More protons adopt the low-energy parallel state and align with B_0, while a few less adopt the high-energy, anti–parallel state.

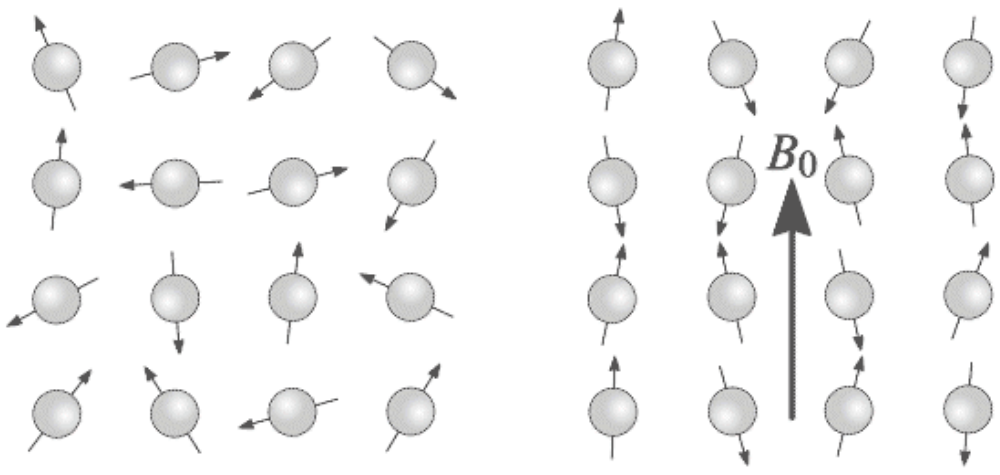

Figure 2: Hydrogen Nuclei

H+ Nuclei (a) Random orientation in the absence of an external magnetic field (b) aligned paralell or anti-paralell to an externally applied field (B0) (from http://www.mikepuddephat.com).

The greater the external magnetic field (B0), the greater the number of spins align in the low-energy, parallel state and the greater the net magnetization differential occurs between the two spin states. This is called the spin excess. In a field containing 10 million protons, only fractionally more protons will align parallel rather than anti-parallel (10,000,007/10,000,000) (McRobbie, Moore et al. 2007). As more protons are in alignment (parallel) with the B_0 field there is a net longitudinal magnetisation parallel to the Z axis of the magnetic field (B_0).

2.2.1.2 **Precession**

Each proton not only spins around its own axis but also the axis of the external magnetic field. This is called precession. The frequency of precession is determined by the characteristics of the spinning proton and the strength of the magnetic field. It is described by the Larmor equation (ReviseMRI.com.):

$$\omega_0 = B_0 * y$$

The symbol ω_0 equals the frequency (radians per second) and γ the gyromagnetic constant (the ratio between the angular momentum and the magnetic moment specific to each element) times B_0 (the external magnetic field). H+ nuclei have a precession frequency of 127.6 MHz in a 3 tesla (3T) scanner (Duggan-Jahns 2008).

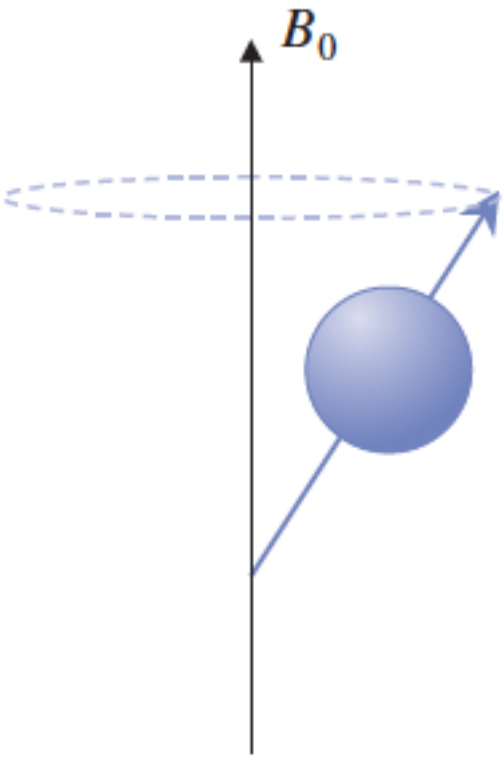

Figure 3: Precession of the H+ nucleus in the magnetic field B_0

(from McRobbie, Picture to Proton (2006) Cambridge University Press).

2.2.2 **Generation Of Mri Images**

2.2.2.1 **Resonance**

In order to produce images, a radio-frequency (RF) pulse (B_1) must be generated. The RF pulse is an oscillating electromagnetic field (radio wave), which is set at the same precession frequency as hydrogen H+ protons. Sending in a pulse at the same oscillation frequency selects H+ protons exclusively, as other protons have different precessional frequencies. Most importantly, the RF pulse causes a phenomenon known as ‘resonance’ in the H+ protons. When exposed to their own oscillating frequency, the hydrogen nuclei gain energy. H+ protons at lower thermal energies (parallel) are able to absorb enough energy to become high-energy protons (anti-parallel).

When the amount of high and low -energy protons are equal, net magnetization along the longitudinal axis decreases or even disappears. This causes a change in the net magnetization vector (NMV) from longitudinal to transverse; the net magnetic moment is flipped from the Z-axis to the x-y plane.

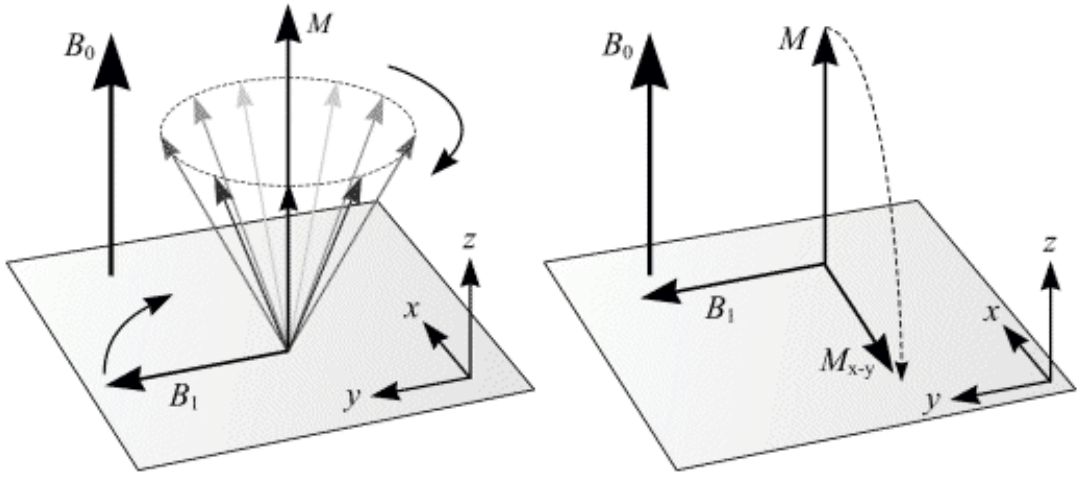

Figure 4: Change in net magnetization vector (NMV) from longitudinal to transverse.

The net magnetic moment is flipped from the Z-axis to the x-y plane (from http://www.mikepuddephat.com).

Protons now also begin to spin ‘in phase’ with each other – this is called phase coherence, as the MDMs of the individual nuclei precess in a synchronized manner. The NMV angle depends on the RF pulse strength and duration. The change in the NMV from a longitudinal to a transverse orientation is called the ‘flip angle’ and a change from longitudinal to 90 degrees is termed a 90-degree flip angle. The transverse magnetization precesses around the B_0 axis. The moving NMV causes an electric current, which is detected by a receiver coil. This is the basis of the MR signal.

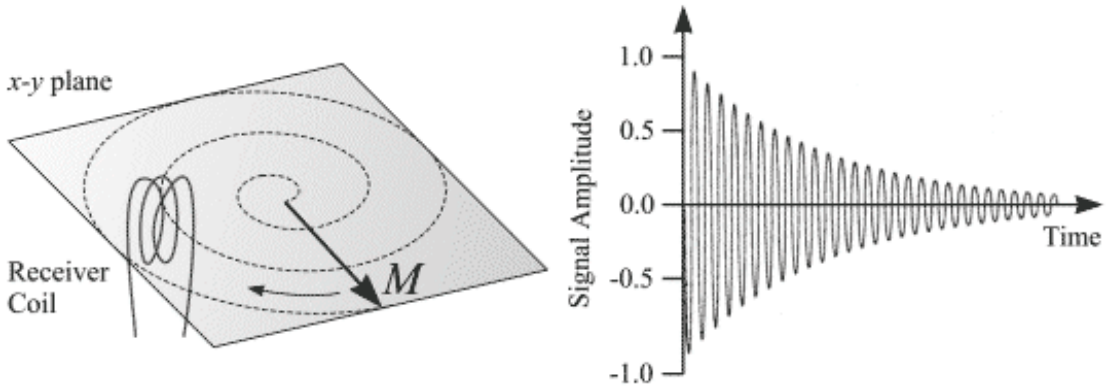

Figure 5: (a) Magentisation in the x-y plane (b) FID

(from http://www.mikepuddephat.com).

2.2.2.2 **After Resonance: T1 Recovery And T2 Decay**

In order to generate an image, the RF pulse is switched off. The electrical signal induced by the transverse NMV is maximal at the instant of switching off the RF pulse, as the NMV is then maximal in the transverse plane at this point. The signal then starts to decay ('relax') as nuclei lose the energy gained by the resonance effect and start to move out of phase with each other once again. The gradual signal loss occurs due to two separate processes – the recovery of longitudinal net magnetization (T1 recovery) and the decay of the transverse net magnetization (T2 decay). T1 and T2 processes are fundamental to the generation of MRI images.

2.2.2.3 **T1 Recovery**

T1 recovery describes the rate of the gradual return to longitudinal magnetization (B_0). When the RF pulse is switched off, the higher thermal

state protons (anti-parallel) release their absorbed energy to the surrounding ‘lattice’ (the molecular environment surrounding the proton - water, fat etc.) and revert towards a low thermal energy, parallel state. The reabsorption of energy to the lattice occurs at different rates, according to the characteristics of the surrounding tissue. Different T1 relaxation times can be used to characterise different tissue types. T1 relaxation is therefore also known as “spin lattice” relaxation and describes the efficiency of the local environment for absorbing the energy of excited protons during relaxation. T1 is a time constant describing when 63% of the original longitudinal magnetization (B_0) has been reached. T1 is a longer process than T2 and takes between 300-3000 milliseconds (T2 takes between 30-150msec).

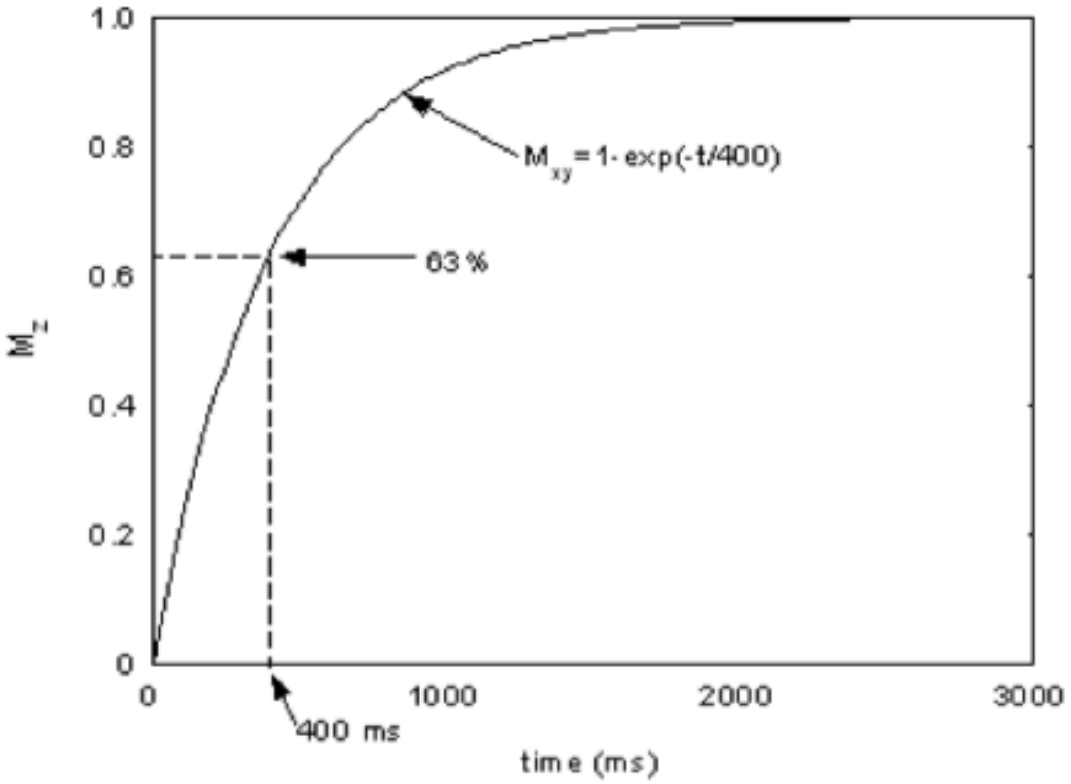

Figure 6: T1 recovery.

Figure shows recovery of the original longitudinal magnetization (B_0). T1 is a time constant describing when 63% original longitudinal magnetization has been reached

2.2.2.4 **T2 Decay**

T2 decay (also called “spin-spin relaxation”) describes loss of phase coherence (‘dephasing’) after the switching off of the RF pulse and the subsequent decay of transverse magnetization. Precession at different frequencies results in loss of phase coherence as the protons drift further apart, with a loss of transverse net magnetic vector and signal to the receiver coil. The greater the homogeneity in the field, the slower the decay and vice-versa.

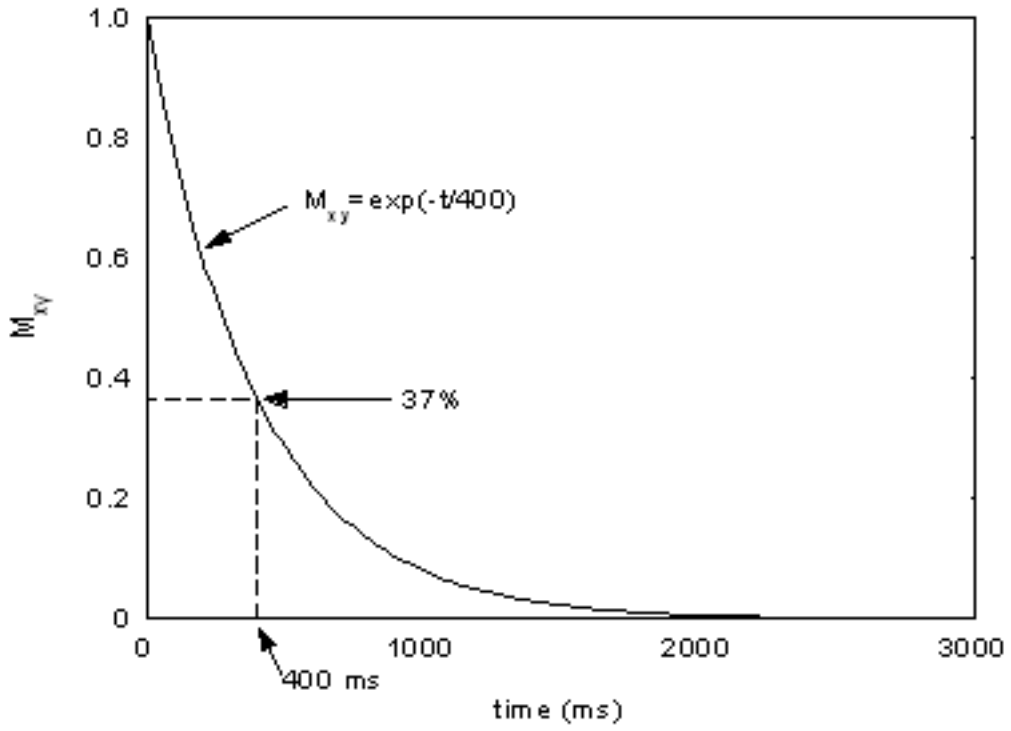

Figure 7: T2 decay.

Image shows time taken for the magnetic resonance signal to decay to 37% of its initial value after its generation by tipping the longitudinal magnetization towards the magnetic transverse plane.

2.2.2.5 **T2* Decay**

Dephasing occurs due to two essential processes. Magnetic fields of adjacent nuclei with different precessional rates act upon each other (spin-spin interaction) causing loss of coherence (intrinsic inhomogeneity). The exponential decay of transverse magnetization caused by spin-spin interactions to 37% of its original value is described by a time constant termed T2. The external magnetic field (B0) also contains variations in its field strength (extrinsic inhomogeneity), which causes H+ protons to have small variations in precessional rates according to their location in the magnetic field. The decay of transverse magnetisation caused by both B_0 inhomogeneity and local tissue inhomogeneity is known as T2*. This process occurs at a faster rate than T2 (spin/spin) relaxation alone. The Free Induction Decay (FID) describes the diminution of the electrical signal produced after the pulse is switched off. Functional imaging relies on the sensitivity of T2* relaxation to different states of oxygenation of venous blood.

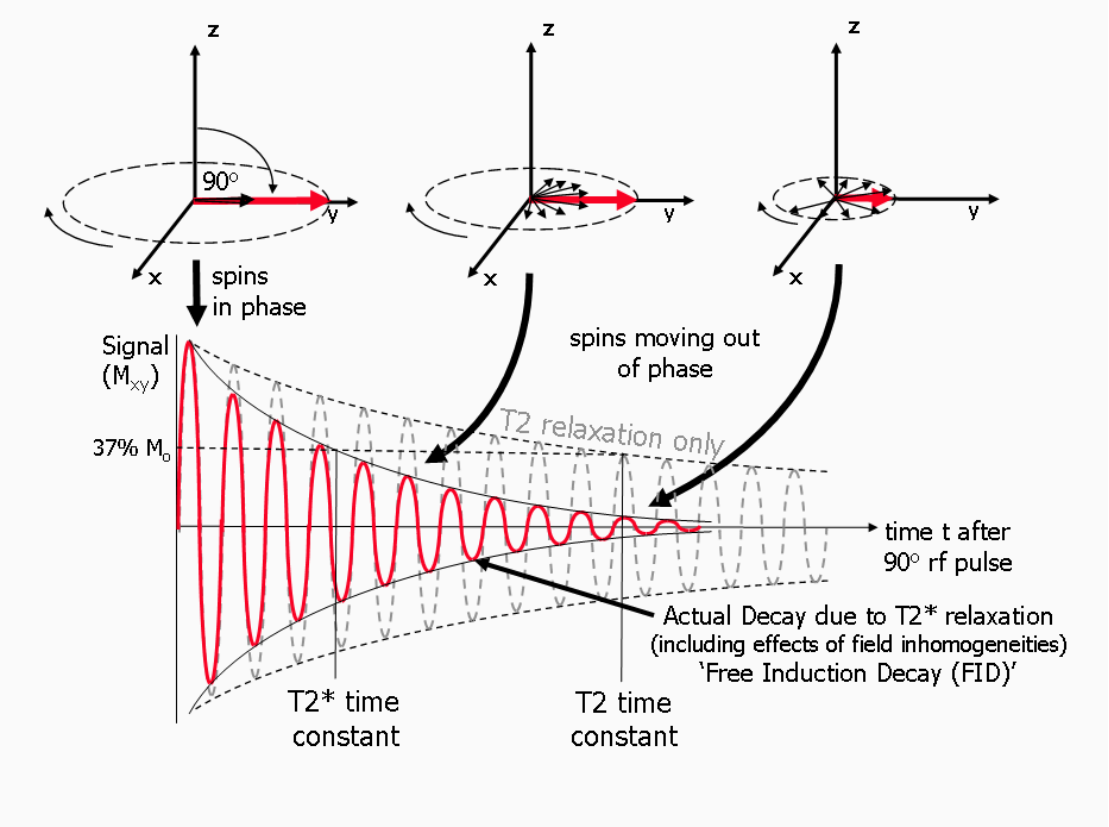

Figure 8 Transverse (T2 and T2*) relaxation processes

Free Induction Decay (FID): Initially, there is maximum amplitude of transverse magnetization as spins rotate in phase. The spins begin to dephase and the amplitude of the net transverse magnetization decays (from: Ridgway *Journal of Cardiovascular Magnetic Resonance* 2010 **12**:71 doi:10.1186/1532-429X-12-71).

2.2.2.6 Using T1 And T2 To Differentiate The Tissues: Contrast Mechanisms

T1 and T2 relaxation rates are not uniform in the body but depend on tissue composition (liquid or solid), structure and surroundings (Damadian and Cope 1974).

With T2 relaxation, the relative inhomogeneities of the tissues influence the rate of relaxation. If the tissues are relatively inhomogeneous, relaxation time

is short. Fatty tissues demonstrate marked differences in magnetic fields between molecules, creating clashing magnetic fields, which cause quick loss of coherence. Therefore T2 relaxation for fat is quick.

Furthermore, fat has a high efficiency for absorbing energy and therefore also has a short T1 relaxation time. Fat contains large molecules, which move relatively slowly and have a high probability for interaction with fluctuating magnetic fields, so energy can be transferred faster. Fat contains carbon bonds at the end of fatty acids with frequencies near the Lamor frequency, which also facilitates a quick transfer of energy. Therefore, T1 time for fat is shorter than for liquids.

In contrast, T2 relaxation of water is long. Water molecules are small and move fast, causing quickly fluctuating magnetic fields that average each other out. This causes no big net differences in magnetic fields and protons therefore stay coherent (in phase) for longer, resulting in greater T2 relaxation times.

Water also has a low efficiency for absorbing energy and therefore also has a long T1 relaxation time. Water (liquid) has many H+ atoms relative to other tissues (i.e. fat). Because it has many H+ atoms, it has a very strong net magnetization vector (i.e. it becomes very strongly magnetized). Water molecules are small and move rapidly making it therefore difficult for protons to get rid of their energy quickly. Therefore T1 relaxation for liquids is slow - water has a long T1 relaxation time.

2.2.2.7 **T1 And T2 Weighting**

By utilising the inherent properties of the tissues and manipulating scanning parameters, an image can be produced that clearly differentiates the different components of the tissues examined (i.e. fluid, fat, bone, white matter, grey matter).

Extrinsic factors are determined by the parameters of the scanner settings. For instance: repetition time of one RF to the next (TR); echo time – time between the pulse and collection of the signal (TE); flip angle (angle of the NMV produced by RF pulse). Intrinsic factors relate to the inherent properties of the examined tissues. For instance: T1 recovery; T2 decay; proton density; flow and apparent diffusion co-efficient.

2.2.2.8 **T1 Weighting**

A T1 weighted image identifies CSF (and liquids) as dark and grey matter (and fat) as bright. It uses a short repetition time (TR) of 300-600ms. TR is a defining feature of T1 weighted images as the TR determines the proportion of longitudinal relaxation that is sampled. Therefore, a short time between pulses does not allow sufficient longitudinal relaxation to occur if the T1 is long. Water and fat both relax at different rates. If the RF pulse is resent quickly (TR short), fat may have relaxed completely and achieved total longitudinal NMV. Therefore, a marked difference in the signal intensity of each tissue will be recorded, according to the amount of longitudinal magnetisation achieved. A longer pause, however between pulses (TR long), allows the longitudinal NMV (T1) of both fat and water to be regained when

the signal is received by the receiver. An image would therefore show no contrast. By also utilising a short TE, little T2 decay will have occurred before measurement and the image will thus depend primarily on tissue T1 relaxation properties.

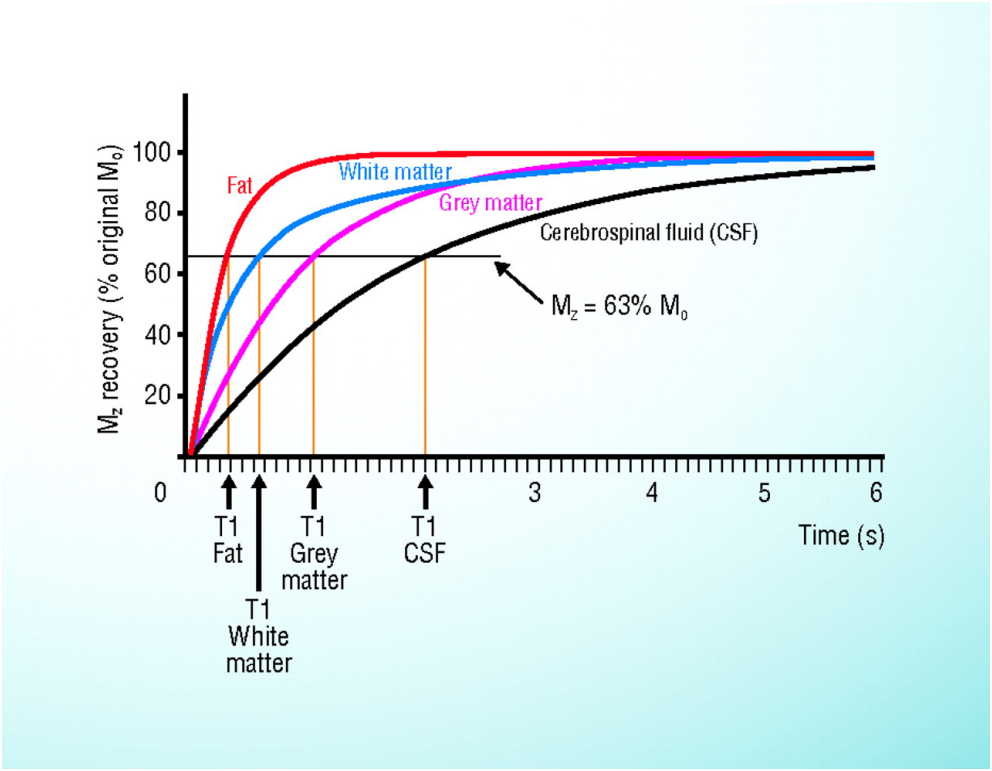

Figure 9: T1 weighting

Relative relaxation rates shown for grey matter, white matter and CSF (from http://mri-2010.blogspot.co.uk/2010/10/october-lecture-notes-1-image-density.html).

2.2.2.9 **T2 Weighting**

By choosing a long TR and TE, the signal can be T2 weighted. A T2 weighted image shows CSF as bright. A long TR allows longitudinal magnetisation to occur fully and therefore T1 will provide no image contrast, allowing imaging contrast to be determined by T2 decay factors alone. TE

parameters determine T2 weighting. A short TE will result in high signal intensity but show little contrast between the tissues, as there will not have been enough time for T2 relaxation to occur. An excessively long TE will allow contrast between the tissues but result in a very weak signal with excess static. The correct TE will result in optimal signal to noise ratio (SNR) whilst still achieving contrast.

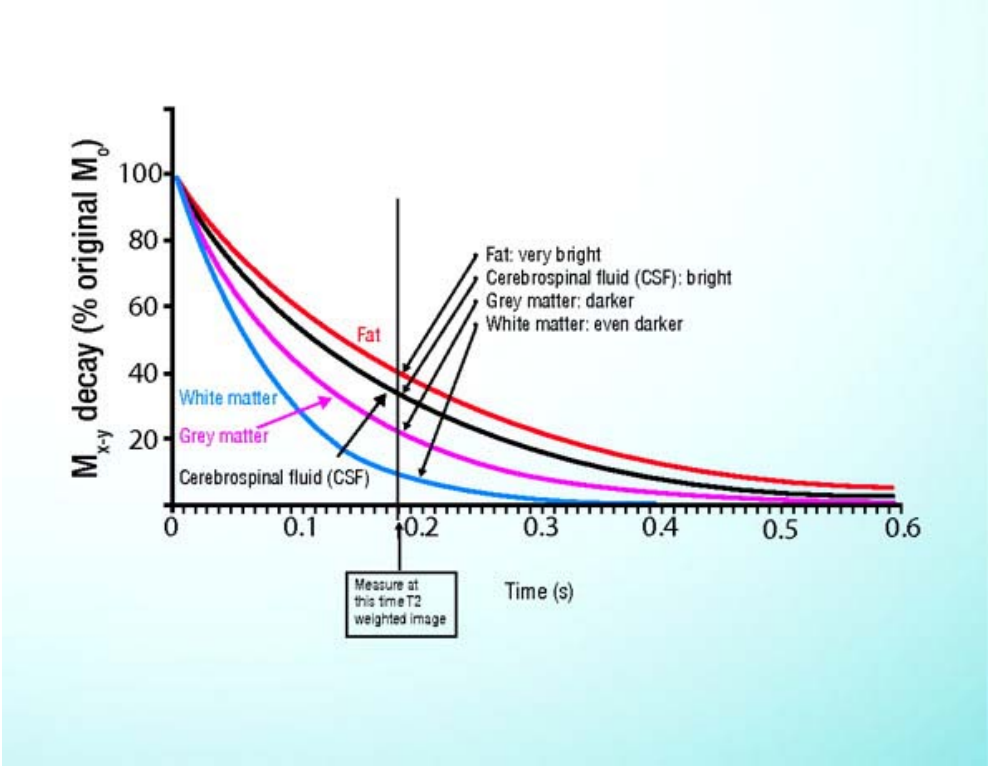

Figure 10: T2 weighting

Relative relaxation rates shown for grey matter, white matter and CSF (from http://mri-2010.blogspot.co.uk/2010/10/october-lecture-notes-1-image-density.html).

2.2.2.10 Uses Of T1 And T2 Scans

Both T1 and T2 weighted scans can be used for structural imaging of the brain. T2* weighted images are particularly relevant in functional imaging.

2.2.2.11 **Image Acquisition: The Spin Echo Sequence**

The spin echo sequence is the most commonly used pulse sequence used to obtain both T1 &T2 weighted images. It is used to counteract the non-uniformities of the magnetic field found in T2* relaxation, so that the images produced reflect differences in the inherent properties of the tissues alone without the influence of inhomogeneity of the external field.

An initial 90-degree pulse (“excitation pulse”) is switched on, causing H+ protons to move in phase on a transverse plane along the X-Y axis. The excitation pulse is then switched off, resulting in a loss of phase coherence due to spin/spin relaxation. Protons fan out at different rates due to external and internal magnetic inhomogeneities. A 180-degree pulse along the Y axis (“refocusing pulse”) is then switched on at TE/2, which causes the protons to now precess in the opposite direction towards the beginning point. Protons precessing at the fastest rates will now be the furthest away. The protons return at the same precessing rates as they went away at, so eventually they all arrive back at the same point in phase. This can be likened to an echo bouncing back off a wall and the sequence is therefore called a spin echo. The signal intensity recorded when H+ protons arrive back at the starting point therefore depends solely on the inherent properties of the tissue itself and not on magnetic inhomogeneities of the external field.

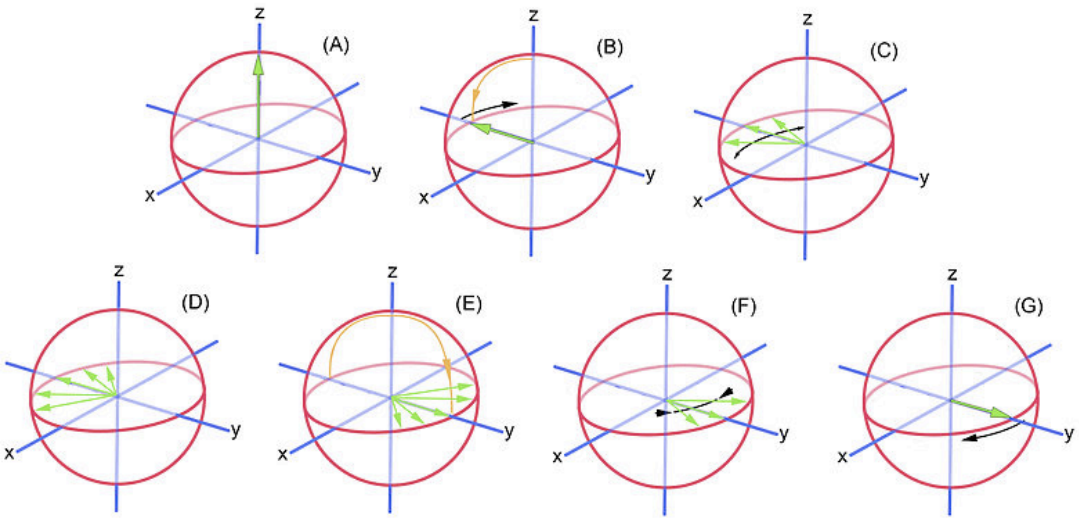

Figure 11: Spin echo sequence

(http://en.wikipedia.org/wiki/File:Spin_Echo_Diagram.jpg).

The process may be repeated in an on-going fashion. Fast Spin Echo (FSE) makes use of multiple 180-degree pulses. Signal intensity declines after each RF application due to internal T2 effects. The curve connecting the declining signal intensities describes a curve known as the T2 curve.

A weakness of spin echo sequences is the necessity of a long repetition time (TR). Reducing the TR would result in faster imaging. However, shortening the TR leaves little time for longitudinal magnetisation to recover, resulting in less transverse magnetisation with each successive flip and therefore successively less signal intensity.

2.2.2.12 Image Acquisition: The Gradient Echo Sequence

A different approach is to use a magnetic field gradient instead of a RF pulse to dephase the spins, which results in considerably faster imaging times.

Initially, a RF pulse is applied using smaller flip angles (10-35 degrees). As a result, the longitudinal magnetisation does not totally disappear when the next pulse is applied.

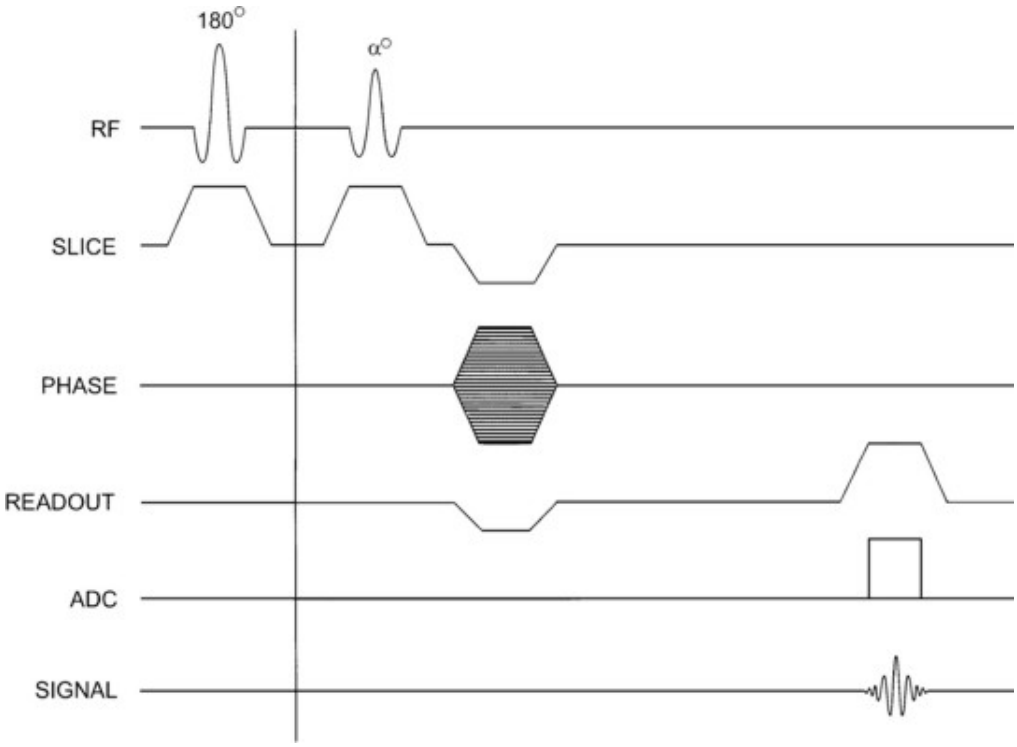

Figure 12: Fig 6; Gradient Echo Sequence (http://bitc.bme.emory.edu/seq_dia.html).

Immediately thereafter, a magnetic field gradient is applied, containing an uneven (small and large) magnetic field, superimposed over the existing B_0. This causes greater inhomogeneity in the external magnetic field (in addition to the existing inhomogeneity of the external field and the local tissues) with subsequent quicker dephasing of protons and decay of transverse magnetization. To reverse the spin dephasing, the magnetic gradient is then turned off and turned on in its opposite direction, causing protons that were

precessing at quicker rates in a strong field to suddenly be exposed to weak fields and therefore move slowly (and vice-versa). Rephasing occurs again to give a maximum signal at the end of the opposite gradient pulse.

2.2.2.13 **Obtaining The Final Image: Magnetic Field Gradients**

In order to generate a spatially specific final image in three dimensions so that the MR signal can be anatomically localised, three magnetic gradient fields (in 3 planes) are superimposed on the existing longitudinal magnetic field (B_0). These are termed the i) Slice selection gradient, ii) Frequency encoding gradient, iii) Phase encoding gradient.

2.2.2.14 **Slice Selection Gradient**

To select a slice perpendicular to the z-axis (for example), a magnetic gradient is applied along the z-axis (from head to toe), resulting in differing magnetic field strengths, causing protons to precess at different frequencies. A RF pulse (called the selective pulse) is then applied at the particular frequency of the gradient to be examined. The selective pulse causes transverse magnetization only of the protons with the same precessing frequency as the pulse and therefore does not affect protons either side of it, which have a different precessing frequency due to the magnetic gradient. Slices of varying thickness can be obtained by altering the bandwidth of the RF pulse (to accommodate more or less of the gradient) or by modifying the steepness of the gradient field. A larger gradient allows more variation in gradient from head to toe, greater variation of precessing frequencies and subsequent choice of selective pulses.

2.2.2.15 **Frequency-Encoding Gradient**

The selective pulse produces rows and columns of protons all precessing in phase at the same frequency. In order to localise signal within a slice, a further magnetic gradient is delivered across the slice (i.e. from L to R) called a frequency-encoding gradient. This causes the columns of protons to dephase at different speeds according to where they are in the gradient (i.e. from L to R).

2.2.2.16 **Phase-Encoding Gradient**

In order to localise to the exact location of each proton within a column, another magnetic gradient field is delivered, known as the phase encoding gradient. This results in different precessing frequencies up and down the column (see previous paragraph). When this gradient is switched off, the nuclei now precess at a regular Lamor frequency in line with B_0 but are out of phase with other nuclei along the gradient. This allows each protons to now be individually identified (Westbrook 2011).

2.2.2.17 **K-Space**

The raw data is acquired (then digitized by the receiver) and stored in a temporal domain commonly called ‘k-space’. K-space is an array of complex numbers of signal intensities encoded by the gradients discussed above. Storage in k-space is determined by the matrices of the frequency and phase-encoding gradients. Low frequency information in the centre of k-space stores information on contrast and larger structures, whereas higher frequency information located at the edges of k-space represents finer detail

and smaller structures. Fourier transformation mathematics, which transform the spatially encoded frequencies stored in k-space allow us to reconstruct the data into the 'image space' with contrast determined by our choice of scanning parameters (Bracewell 1986, Gallagher, Nemeth et al. 2008)

2.3 **Statistical analysis**

2.3.1 **Statistical Parametric Mapping (Spm)**

Statistical Parametric Mapping (SPM) refers to the construction of spatially extended statistical processes used to test hypotheses about regional specific effects in imaging data (Friston, Frith et al. 1991). In this thesis, SPM refers to the implementation of these voxelwise statistical processes using 'SPM' software (http://www/fil.ion.ucl.ac.uk/spm), however alternative software packages for example the 'FMRIB Software Library (FSL)' and 'Analysis of Functional Neuroimages (AFNI)' are built upon similar spatial statistical frameworks. SPMs can be used to examine volumetric, and functional activation differences between groups or experimental states within-group using voxelwise (mass-univariate) independent statistical tests on every single voxel to produce probability density function maps under the null hypothesis (T- or F-maps) that are fashioned into an image or 'map'. SPM maps are often interpreted by referring to the probabilistic behaviour of Gaussian random fields (Worsley and Friston 1995).

2.3.2 **The General Linear Model**

The General Linear Model (GLM) is a statistical model used in the analysis of MRI data, which attempts to model the scanner data into components of interest, confound and error. The GLM encompasses common statistical tests used in MRI such as t-test, analysis of variance (ANOVA) and multiple regression analysis. It makes inferences about the effects of interest in relation to the error variance, in order to arrive at an F statistic or similar estimate of probability (for a review, see http://www.fil.ion.ucl.ac.uk/spm and (Smith 2004)).

The GLM can be expressed as a formula (employed at every voxel):

$$Y = X\beta + c + e$$

Y is the observed data from the scanner (dependent variable), measured as intensity at every voxel. ***X*** are regressors (dependent or predictor variable), which represent the experiment design variable. Regressors of interest are variables expected to explain the data (ie the experimental manipulation). Regressors of no interest (nuisance variables) are confounding variables that are not part of the experimental design or variables beyond reasonable experimental control (for example, head motion, age, gender). ***β*** is the estimated parameter value (i.e. the optimal value required to make ***X*** fit to ***Y***, such that the error ***e*** is minimised). The error or 'residual' term, ***e*** is the difference between the observed data, ***Y***, and that predicted by the model, ***Xβ***. ***c*** is a constant term that expresses the value of the intercept.The optimal

parameter estimates, $\boldsymbol{\beta}$, are found by minimising the sums of squared differences between the predicted model and the observed data. To put it simply, the best estimates $\boldsymbol{\beta}$ are those that minimise the amount of unexplained data in the model.

In standard MRI analysis the GLM is represented by a *design matrix* expressed as a series of columns, each containing a regressor (explanatory variable) $\boldsymbol{x}$ that is intensity coded for its relative contribution to $\boldsymbol{y}$. (see Figure 13)

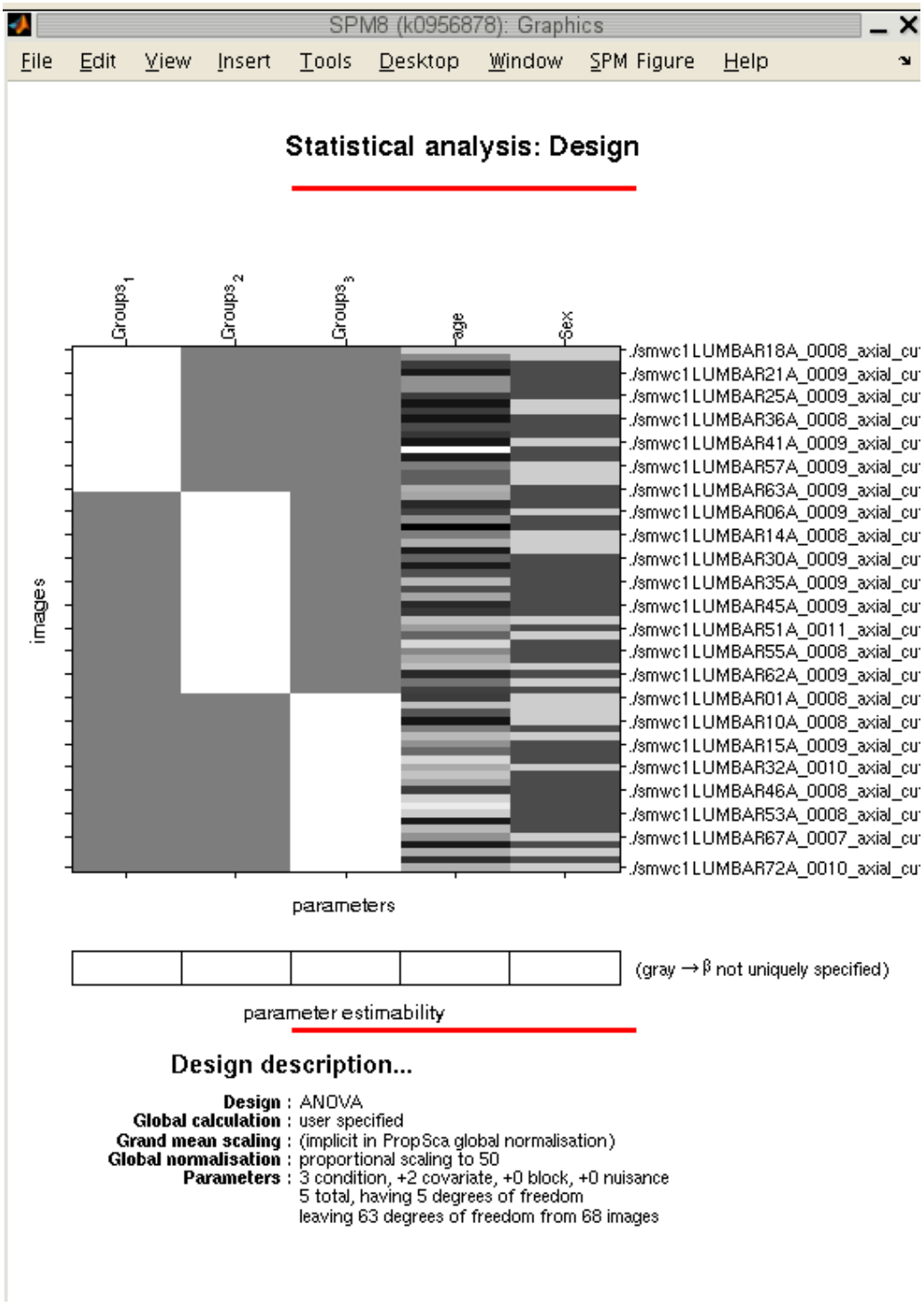

Figure 13: VBM design matrix.

The X axis describes the three groups in the study and two regressors (age and gender). The Y-axis relates to each individual subject's scan. The relative contributions of the regressor of each subject are expressed by the intensity of shading. For instance, relative age is from light grey to black whereas gender is expressed in tow tones only.

Parameter estimates ***β*** are compared with the uncertainty in their estimation in order to arrive a ***T*** value for each voxel. The ***T*** value is the parameter estimate (***PE***) divided by the standard error (***SE).*** High or low values of the PE in relation to its estimated uncertainty will give high or low ***T values*** respectively. In the simplest case of a one-sample t-test, the value of ***T*** is an indicator of how likely the ***PE*** is to be significantly different from zero (i.e. whether there is significant activation in an fMRI task, CBF change in an ASL investigation or a tissue volume difference in a VBM study).

2.3.3 **Creation Of Contrasts**

Parameter estimates can be used to test the relevant contributions of one regressor in a model compared to another by simple subtraction of one regressor to another compared to their combined standard error. These 'so-named' 'contrasts of parameter estimates' or 'contrasts' are expressed in SPM as a simple [-1, +1]. A T-statistical map is then generated, which graphically represents the distribution of differences between regressor 1 and regressor 2 across the volume of interest (Smith 2004).

2.3.4 **Inference**

Having obtained a statistical T map composed of scores for every voxel in the brain, it is then necessary to set a statistical threshold, at a given level of significance (***Z*** or p-value), in order to make inferences as to which parts of the brain show significant activation (or in VBM, which voxels show

significant GM loss or gain). An inference is made that voxels with T scores above a stated threshold will reject the null hypothesis.

Three levels of inference are available for whole brain MRI analysis: set-level, voxel-level and cluster-level (Poldrack 2011). Set-level inference merely states if there are clusters in the T map that pass significance according to the p-value. Cluster-level significance is determined by the number of contiguously activated voxels in an area (spatial extent) and to some extent the peak height, and therefore gives sensitivity to spatially extended signals (Friston, Holmes et al. 1996, Poline, Worsley et al. 1997) compared to voxel-level inference, where the peak height alone is the determining factor (see figure 14).

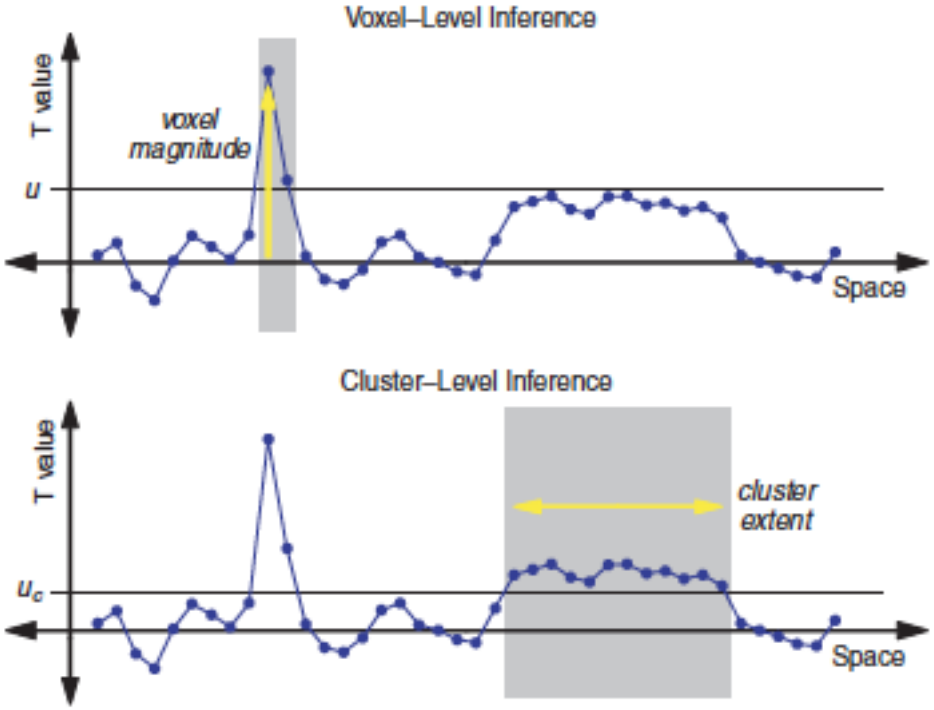

Figure 14: Voxel-level versus cluster-level inference.

The above image illustrates voxel-level inference - two voxels are identified above a significance threshold and both are marked as significant. The image below illustrates cluster-level inference - a series of voxels is identified as a significant cluster although none would pass significance based on height threshold alone (adapted from (Poldrack 2011).

2.3.5 **Multiple Comparisons Correction**

Conventionally, the statistical significance level is set at 5% (p value of 0. 05). Setting a p-value of 0 05 assumes that there is 5% probability that the same result could happen by chance, giving a false positive result (Type-1 error). Therefore, a T score with an associated significance level of 0.05 %, applied to a mass-univariate statistical analysis of MRI data involving 100,000 voxels, is liable to introduce approximately 5000 false positive voxels (even if the null hypothesis is accepted). With an abundance of false positive data, how can a threshold be set that allows confidence that the suprathreshold voxels are not merely due to chance? Statistical correction is

therefore necessary to account for Type-1 error when dealing with multiple statistical comparisons in MRI analysis (Bennett, Wolford et al. 2009, Poldrack 2011).

2.3.5.1 **Bonferroni Correction**

The standard statistical approach to multiple testing is to correct the p-thresholds to account for how many tests are being done. For instance, Bonferroni correction works by dividing the desired p value by the number of comparisons. For analysis of 100,000 voxels, this arrives at 0.05/100,000 = $p < 0.0000005$ at every single voxel. The Z score associated with this p-value, which we would use as a threshold, would be very large. Whilst this undoubtedly controls the occurrence of false positives, it is far too stringent (conservative) and is liable to result in type II errors (false negatives) with loss of significant data (Jezzzard 2001, Smith 2004, Lindquist 2008).

2.3.5.2 **Spatial Correlation Of Data**

Bonferroni correction requires data (voxels) to be independent of each other (and therefore that tests performed and resulting z scores are independent of each other). Spatial correlation of MRI data violates this assumption. MRI data is frequently spatially correlated, in that data from one voxel will tend to be similar to data from nearby voxels. This is due to several factors including: (i) spatial smoothing of data, which reduces the number of independent data points by averaging across voxels; (ii), the likelihood that contiguous voxels frequently work together in group activation; (iii) partial voluming effects due

to re-slicing of images during pre-processing causing smoothing across voxels

2.3.5.3 **Gaussian Random Field Theory (GRF) And Family-Wise Error:**

Bonferroni correction is calculated based on the number of truly independent voxels. If one were able to calculate the true number of independent voxels, it would be possible to use Bonferroni. However it is not possible to work out how many independent observations there are in smoothed data. Commonly in analysis of neuroimaging data an alternative method, named Gaussian Random Field theory (GRF) is adopted as an approach to overcome the multiple comparisons problem (Worsley, Evans et al. 1992).

GRF estimates the number of resolution elements (resels) in smoothed data. A resel is essentially a cube of voxels of the same size as the full width half maximum (FWHM) Gaussian kernel used to smooth the data. The resel count is used to estimate how many significant clusters should be found according to chance at a given statistical threshold; this is known as the expected Euler characteristic (EC). When the statistical threshold is set high, the EC will be correspondingly low. The expected EC is a good approximation of the probability of observing one or more clusters at a certain threshold. For instance, a Z score of *x* that gives an EC of 0.05, indicates that any clusters passing threshold will have a probability of less than or equal to 0.05 of having occurred by chance. Although GRF can be thought of as a Bonferroni-type correction that allows for multiple non-independent tests due to spatial correlation (smoothness) it is not the same and GRF produces corrections that are more liberal.

2.3.5.4 **Non-Stationary Cluster Extent Correction**

Gaussian Random Field theory performs statistical corrections based on the assumption that data is uniformly smooth across the whole brain in a Gaussian distribution. GRF theory is valid for corrections based on peak heights (voxel-wise) but not for corrections based on cluster extents, due to anisotropic smoothness of the data, which is non-stationary (i.e. not the same) across regions of grey matter (GM) and white matter (WM). Assumptions of stationary smoothness produce invalid cluster-level statistics - cluster sizes will be overestimated in smooth areas (type 1 error) and underestimated in rough areas (type 2 error) (Worsley and Friston 1995, Hayasaka and Nichols 2004). This has lead to recommendations to abandon the use of cluster-size tests in VBM (Ashburner and Friston 2000). In fact, the assumption of stationarity in fMRI data has also been questioned (Hayasaka, Phan et al. 2004).

Therefore, in order to arrive at valid cluster size statistics, we have adopted the method proposed by Hayasaka et al (Hayasaka, Phan et al. 2004) to correct for issues of non-stationarity, using the toolbox developed for the VBM toolbox in SPM8 by Christan Glaser at the University of Jena (see http://dbm.neuro.uni-jena.de/vbm/non-stationary-cluster-extent-correction/).

Chapter 3 CHARACTERISATION OF CHRONIC LOW BACK PAIN: BEHAVIOURAL EVALUATION AND SENSORY EXAMINATION

3.1 Introduction

I will adopt a model of pain throughout this thesis which is centred not only on the sensory-discriminative experience of the patient but also on cognitive-evaluative, and affective-motivational mechanisms, rather on pathological mechanisms alone. The experience of pain is more than purely sensory; pain incorporates cognitive and emotional aspects, which mediate the *distress* felt by sufferers of chronic pain. This distress, which includes psychological components of increased anxiety, bodily awareness, and depression, may in itself, increase and perpetuate chronic pain (Lumley, Cohen et al. 2011).

3.1.1 Body Identity And CLBP

It has been claimed, however, that the study of the psychology of pain has neglected the body, preferring to concentrate on the mind as a 'disembodied' abstract concept (Kelly and Field 1996). Unlike other forms of sensory stimuli, which are experienced externally, pain is experienced within the body: embodiment.is central to notions of self-identity, self-agency and self-worth (Corbin 2003, Osborn and Smith 2006) - "The body is the embodiment of who we are" (Corbin 2003). In a study asking patients to describe their experience of CLBP, subjects contrasted a 'previous' body associated with

their ‘original’ healthy self, with a ‘new’ dsyfunctioning body associated with their present identity as a sufferer of CLBP. Previously, when pain free and fully functional, patients reported being largely unaware of, and uninterested in, the internal workings of the body. However, the painful ‘new’ body had to be constantly assessed and monitored; activities of daily living had gone from being effortless and thoughtless to “planned, fearful and threatening” (Osborn and Smith 2006). The authors suggested patients’ experience was akin to Pincus and Morley’s concept of “enmeshment”, in which pain in the body became entangled with a rejected and negative view of the self, forming an “enmeshment” from which the patient could not free themselves (Pincus and Morley 2001).

3.1.2 **CLBP Sufferers Experience A Fundamental Change In Relationship With Their Body**

CLBP sufferers experience a fundamental change in relationship with the “new” body. In spite of the novel attention to the workings of the body, patients paradoxically report feeling alienated from the ‘new’ body. The painful back feels different to the rest of their body, as if it was not working for them, even that it no longer felt part of them. Patients had a concept of their ’best/preferred self’ from which they were alienated or excluded. Alienation from, or rejection of, certain body parts (neglect) is a common symptom of overt neurological damage such as stroke. Patients demonstrate little appreciation of the shape, contour and position in space of their own bodies (Husain 2008). Neglect-like symptoms have also been reported in other chronic pain conditions (Galer and Jensen 1999, Schwoebel, Friedman

et al. 2001, Flor, Nikolajsen et al. 2006, Frettloh, Huppe et al. 2006, Lewis, Kersten et al. 2007, Vartiainen, Kirveskari et al. 2009, Lewis, Kersten et al. 2010, Foell, Bekrater-Bodmann et al. 2013) including LBP (Moseley 2008, Moseley, Gallagher et al. 2012).

3.1.3 Altered Body Schema And Disruption Of Cortical Maps Are Seen In CRPS, PLP And CLBP

Neglect-type symptoms and changes in perceptual disorders imply accompanying neuroplastic changes to the central nervous system. Normal body schema is dependent on both regular somatosensory and proprioceptive input and motor output. In CRPS and PLP, altered afferent input, both painful and non-painful, is linked to disruption of motor (M1) and sensory (S1) cortical representational maps (Moseley and Flor 2012). Similar disruption of cortical representational maps are seen in CLBP using magnetoencephalography (MEG) (Flor, Braun et al. 1997) and fMRI (Lloyd, Findlay et al. 2008). Both studies show a medial shift in the representation of the back in the somatosensory cortex suggesting a functional neuroplastic alteration.

3.1.4 Changes In Body Schema Are Associated With Alterations In Two-Point Discrimination (2PD) In CRPS, PLP And CLBP

Changes in tactile acuity (defined as “the keenness or sharpness of the sense of touch, usually measured by the two-point threshold” (Colman

2008)) have been demonstrated in patients with a variety of chronic pain conditions (Flor, Denke et al. 2001, Wand, Di Pietro et al. 2010, Stanton, Lin et al. 2013). Studies, using a variety of methods (MEG, EEG (electroencephalography) and fMRI show that alterations in 2PD are associated with changes in representational maps in the motor and somatosensory cortex, in patients with CRPS (Flor 1995, Juottonen, Gockel et al. 2002, Maihofner, Handwerker et al. 2003, Pleger, Tegenthoff et al. 2004, Maihofner, Forster et al. 2005) and PLP (Flor, Elbert et al. 1995, Lotze, Flor et al. 2001).

Two-point discrimination (2PD) is the most widely used test in the assessment of tactile acuity. Traditionally, the test is thought to measure the density of nerve fibre regeneration after injury (Weinstein 1993) in particular the concentration of slowly adapting type 1 fibres, which are selectively sensitive to spatial discontinuities (Johnson and Hsiao 1992). However, advances in the understanding of supraspinal plasticity in relation to somatosensory cortical representation have suggested alternative uses for 2PD testing. It has been noted that in normal subjects, there is a wide variation of normative values for 2PD discrimination throughout the body, from 2-4mm on the fingertips to 50mm or more on the trunk (Nolan 1985).These variations reflect not only peripheral innervation density but also representational maps in the somatosensory cortex; areas with reduced innervation density (and therefore large 2PD thresholds) also demonstrate reduced representation of the body part in the S1 somatosensory cortex (Kandel 2012). Furthermore, 2PD thresholds are sensitive to training effects.

Healthy individuals demonstrate decreases in 2PD thresholds after only a few hours of training (Godde, Stauffenberg et al. 2000). It is therefore highly unlikely that observed changes in sensory thresholds are due to in changes in sensory receptive field density due to neurogenesis. Rather, it has been suggested that changes in 2PD thresholds are more likely due to central nervous system neuroplasticity of cortical representational maps. Enlargement of cortical representation of the index finger has been shown after a short period of 2PD training (Pleger, Dinse et al. 2001, Godde, Ehrhardt et al. 2003). Pharmacological modulation with both memantine and methamphetamine (NMDA receptor agonist and anatagonist respectively) correlates with representational changes in the S1 cortex, suggesting a synaptic basis for the change in these receptive fields (Dinse, Ragert et al. 2003). Furthermore, reorganisation of S1 representational maps correlates not only with the intensity of pain (Flor, Elbert et al. 1995, Maihofner, Handwerker et al. 2003, Maihofner, Forster et al. 2005) but has also been shown to correlate with alterations in tactile acuity (Pleger, Tegenthoff et al. 2005, Pleger, Ragert et al. 2006).

Chronic low back pain is also associated with disturbances of sensory perception. Initial data suggest that CLBP patients report significantly larger 2PD thresholds than controls on the lumbar spine, although normal 2PD thresholds are found elsewhere on the trunk and tactile thresholds are unaltered (Moseley 2008, Wand, Di Pietro et al. 2010, Luomajoki and Moseley 2011). As yet there is no data directly linking alterations in sensory discrimination in CLBP with altered cortical representation. I have therefore

chosen to use 2PD as a methodology to assess the impact of CLBP on supraspinal somatosensory representation. Later chapters in this thesis will assess the neural correlates of these examination findings utilising neuroimaging methodologies.

3.1.5 Proprioceptive And Motor Control Disorders Are Also Associated With Altered Two-Point Discrimination In CLBP

Proprioceptive deficits and motor control disorders are frequently seen in patients with CRPS and PLP (Anderson-Barnes, McAuliffe et al. 2009, van Rijn, van Hilten et al. 2009). It has been suggested that these deficits are related to altered central processing of proprioceptive information (Bank, Peper et al. 2013). Deficits in motor control, muscle activation and poor proprioceptive acuity of the lumbo-pelvic region, frequently seen clinically in CLBP patients, (for a review see (Hodges and Moseley 2003)) also show a close association with increased 2PD thresholds on the back (Moseley 2008, Wand, Di Pietro et al. 2010, Luomajoki and Moseley 2011). These changes have been linked to changes to M1 representational maps (Tsao, Galea et al. 2008, Tsao, Danneels et al. 2011, Wand, Parkitny et al. 2011). As yet there is no data directly linking proprioception and motor dysfunction in CLBP with altered cortical representation.

Furthermore, not only are CLBP patients unable to perform proprioceptive tasks skillfully, they also demonstrate less skill than controls in recognising the movement orientation of others, in common with patients with CRPS.

CRPS patients perform poorly on a hand laterality recognition task, which has been proposed to be related to disrupted body schema, and altered cortical networks (Moseley 2004). In a similar experiment with CLBP patients, subjects were unable to accurately judge the direction of trunk rotation (left or right) adopted by a model. The degree of accuracy was related to the spread of patients' lower back pain. In patients, accuracy for left/right trunk rotation judgment was 53.4% (44.5% to 62.3%) and 67.2% (60.2% to 74.1%) for those with bilateral and unilateral presentations respectively. Pain-free control participants were able to distinguish left and right with an accuracy of 87% (75-98%). All three groups were highly accurate in a left/right-hand identification task ("about 83% of the time"), which indicates that disruption of the body schema is most likely specific to the condition and to the area of dysfunction (Bray and Moseley 2011).

3.1.6 **Perceptual Challenges In CLBP**

In addition to perceptual difficulties in recognising the movement orientation of others, there is evidence that CLBP patients may face perceptual challenges related to their own bodies. Many patients who have suffered overt neurological damage such as stroke (and frequently conditions such as CRPS and PLP) demonstrate little appreciation of the shape, contour and position in space of their own bodies (Moseley 2008) Some CLBP patients also report similar symptoms, in not being able to recognise their back as a part of themselves - "not me" (Osborn and Smith 2006).Some CLBP patients are also unable to clearly delineate the outline of their own back when asked to draw it. Importantly, association was found with poor tactile acuity

measured using two point discrimination supporting the potential importance of this sensory testing modality to reveal supraspinal representational change (Moseley 2008).

It has been proposed, therefore, that the changes outlined above, provide evidence that CLBP is linked to disruption of the virtual representation of the body in the motor and sensory cortex, and that CRPS and CLBP may therefore share similar neural mechanisms (Luomajoki and Moseley 2011).

3.1.7 What Factors Underlie Alterations In 2PD And Representational Change?

It, is unclear, however, what factors underlie representational change. It appears unlikely that the mechanism for 2PD is due to disrupted or delayed transmission along the neuraxis, as transmission of normal cutaneous input to S1 in CLBP patients is unaffected (Flor 2003). Tactile thresholds are also normal (Moseley 2008, Wand, Di Pietro et al. 2010). It has been suggested that poor 2PD performance may be due to central sensitization mechanisms causing spinally-evoked noxious input to result in supraspinal noise and a loss of normal inhibition (Luomajoki and Moseley 2011). Therefore, I suggest that increased 2PD thresholds on the trunk in CLBP are most likely linked to reorganization of representational maps that have been shown in CLBP and also in PLP and CRPS.

Relationships between 2PD, representational change and components such as pain intensity, chronicity, emotions, cognitions, medication or lifestyle

changes are difficult to establish and there is a lack of consistency amongst studies in reporting these relations. For instance, although representational change in below-level spinal cord injury (SCI) injury pain correlates with pain intensity (Wrigley, Press et al. 2009) others studies have found that changes relate not to pain intensity but to chronicity instead (Lotze, Laubis-Herrmann et al. 2006). Similarly, studies have shown that alterations in S1 representation of the affected limb in CRPS (Maihofner, Handwerker et al. 2003, Pleger, Tegenthoff et al. 2004) and PLP (Flor, Elbert et al. 1998, Grusser, Winter et al. 2001, Karl, Birbaumer et al. 2001) are associated with pain intensity. Furthermore, normalisation of the cortical representation of the 1st and 5th fingers in CRPS (Maihofner, Forster et al. 2005) and of the lip and hand areas in PLP is associated with reduction of pain in fMRI studies (Lotze, Flor et al. 2001). In CLBP, however, the medial shift of the trunk, reported by Flor in 1997 was associated with pain duration and not intensity (Flor, Braun et al. 1997). Further analysis of the neural mechanisms underlying CLBP and relationships with psychological and sensory discriminative examination variables is needed.

3.1.8 **Chapter Summary**

The purpose of this chapter is to quantify the emotional-motivational, cognitive-evaluative and sensory-discriminative characteristics of CLBP patients compared to controls and, in particular, NuLBP and MLBP subgroups using questionnaire-based evaluation and clinical examination of tactile acuity. There are five main hypotheses to be tested in this study:

1) Patients with CLBP exhibit greater psychological distress compared to controls

2) Patients with NuLBP complain of greater pain and psychological distress compared to MLBP patients

3) CLBP patients demonstrate altered two-point sensory discrimination thresholds and tactile thresholds of the lower back compared to controls

4) NuLBP exhibit altered two-point sensory discrimination thresholds and tactile thresholds compared to MLBP patients

5) Deficits in sensory discrimination are related to the severity and/or duration of symptoms.

3.2 **Methods**

3.2.1 **Psychometric And Behavioural Data**

The following questionnaires were administered in order to assess pain and psycho-physical status: Numeric rating scale (NRS) for pain, Short Form McGill Pain Questionnaire (SFMPQ) (Melzack 1987), RAND Medical Outcomes 36-Item Short Form Survey Instrument (SF-36) (Ware and Sherbourne 1992), Centre for Epidemiologic Studies Depression Scale Questionnaire (CES-D) (Radloff 1977); State Trait Anxiety Inventory (STAI) (Spielberger 1983), Revised Symptom Checklist 90 Questionnaire (SCL-90-R) (Derogatis and Unger 2010), Eysenck Personality Questionnaire (revised version) (EPQ-R) (Eysenck, Eysenck et al. 1985), painDETECT Questionnaire (Freynhagen, Baron et al. 2006).

3.2.1.1 **Numeric Rating Scale (NRS) For Pain**

All patients had LBP for at least 12 months. Patients rated their pain on a numerical rating scale (NRS) at screening and on the day of scanning. The NRS is an 11 point numeric version of the visual analog scale (VAS) in which a subject chooses a whole number between 0 -10 that corresponds to the intensity of their pain. The numbers are arranged along a horizontal line and anchored by the terms 0=“no pain” to 10 “maximum pain”. The NRS is used widely in chronic pain studies due to its brevity and ease of use for patients (Farrar, Young Jr et al. 2001).

3.2.1.2 **Short Form Mcgill Pain Questionnaire (SFMPQ)**

The SFMPQ is a multidimensional measure of pain, which has been modified from the original version of the McGill Pain Questionnaire (Melzack 1987). It is composed of eleven sensory and four affective pain descriptors, rated on an intensity scale from 0 (none) to 4 (severe). The two-factor structure has been cross-validated in a large sample of CLBP patients (Beattie, Dowda et al. 2004). It also includes a 10-cm visual analogue scale (VAS) and a five-item present pain intensity scale (PPI) to describe overall pain intensity (Turk and Melzack 2011). It has had widespread use in adult chronic pain populations, including CLBP (Ruoff, Rosenthal et al. 2003) and has modest predictability in discrimination of neuropathic and musculoskeletal pain of spinal cord injury (Putzke, Richards et al. 2002).

3.2.1.3 **Rand Medical Outcomes 36-Item Short Form Survey Instrument (SF-36)**

The SF-36 uses 36 questions to assess eight health concepts (Ware and Sherbourne 1992): 1) limitations in physical activities because of health problems (SF-36 Physical Function); 2) limitations in social activities because of physical or emotional problems (SF-36 Social Function); 3) limitations in usual role activities because of physical health problems (SF-36 Role-Physical); 4) bodily pain (SF-36 Pain); 5) psychological distress and emotional well-being (SF-36 General Mental Health); 6) limitations in usual role activities because of emotional problems (SF-36 Role-Emotional); 7) energy and fatigue (SF-36 Vitality); 8) general health perceptions (SF-36 General Health). For each of the eight domains an aggregate percentage

score is produced. The percentage scores range from 0% (lowest or worst possible level of functioning) to 100% (highest or best possible level of functioning). Two summary scores of physical quality of life (Physical Component Summary; PCS) and psychological well-being and general health perception (Mental Component summary; MCS) can also be obtained by combining physical and mental domains respectively (Ware, Kosinski et al. 1995). PCS and MCS scales are scored to have the same average (50) and standard deviation (10) (norm-based scores). Therefore scores below and above 50 represent above and below average values of physical and mental health and functioning with increasingly low scores represent increasing degrees of psychological distress and disability (Ware 1993). A cut off score of 35 or less on the MCS is able to identify depressive symptoms (as measured by the CES-D) in LBP patients (Walsh, Homa et al. 2006).

3.2.1.4 Centre For Epidemiologic Studies Depression Scale Questionnaire (CES-D) Questionnaire

The CES-D is a 20-item questionnaire of symptoms associated with depression (Radloff 1977) that demonstrates good sensitivity and specificity and high internal consistency (McDowell 2006). Scores range from 0 to 60, with high scores indicating greater depressive symptoms. It cannot be used to diagnose depression in itself. However, scores of 16 or greater can be used to identify individuals at risk for clinical depression in primary care and 19 or greater in the chronic pain population (Turk and Okifuji 1994).

3.2.1.5 **State Trait Anxiety Inventory (STAI)**

The STAI is a 40-item questionnaire that measures two components of anxiety: Anxiety in the present moment ("state") and anxiety as a general, ongoing personal characteristic ("trait"). Twenty questions are each scored on a four point Likert scale and higher scores are associated with higher levels of anxiety. The STAI has good reliability, validity, and sensitivity (Quek, Low et al. 2004). CLBP subjects have previously demonstrated increased trait anxiety levels compared to acute LBP subjects (Newcomer, Shelerud et al. 2010). Fear avoidance beliefs have also been associated with anxiety and CLBP (Gatchel, Polatin et al. 1995, da, Maher et al. 2012).

3.2.1.6 **Revised Symptom Checklist 90 Questionnaire (SCL-90-R)**

The SCL-90-R is a 90-item questionnaire designed to assess a broad range of psychological problems and the current psychopathology of subjects along nine symptom constructs; Somatization, Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic-Anxiety, Paranoid Ideation and Psychoticism). Three additional scales have also been developed; the Positive Symptom Total (PST) measuring the total number of self reported symptoms, the Positive Symptom Distress Index (PSDI) measuring intensity of symptoms and the Global Severity Index (GSI), designed to measure overall psychological distress which can be used as a summary of the test (http://www.pearsonassess.ca). The SCL-90-R has been widely used in CLBP (Bernstein, Jaremko et al. 1994, Viniol, Jegan et al. 2013).

3.2.1.7 **Eysenck Personality Questionnaire (EPQ)**

The Eysenck Personality Questionnaire (revised) (EPQ-R) is a one hundred yes/no question scale that measures personality in three dimensions; extraversion/introversion, neuroticism/stability, psychoticism/socialization (Eysenck, Eysenck et al. 1985). It has been widely used in a variety of medical and psychiatric settings. The neuroticism and extraversion scales of the EPQ-R show very good internal consistency and consistency over time although the psychoticism scale is characterized by a somewhat lower internal consistency (Irving B. Weiner 2010)

Extraverted individuals with high EPQ-R-E scores tend to be outgoing, impulsive and uninhibited. They enjoy socialising and dislike solitary pursuits. They tend to be active, seek out excitement and enjoy group activities. Individuals with high neuroticism scores (EPQ-R-N) tend towards emotional lability and often complain of generalised anxiety and worries and negative emotions. They may complain of ongoing somatic symptoms. Individuals with high psychoticism scores tend towards hostility and aggression towards others with a lack of empathy. However high scores do not in themselves imply that the individual is psychotic in the full-blown psychiatric sense of the term, solely that the individual has tendencies in that direction and therefore, the term “tough-mindedness” is often substituted. The neuroticism and extraversion scale s of the EPQ-R show very good internal consistency and consistency over time although the psychoticism scale is characterized by lower internal consistency.

3.2.2 **Clinical Examination: Sensory Testing**

2PD and TTD (Tactile threshold discrimination) testing was carried out on all subjects. Participants were positioned comfortably in prone lying with a pillow underneath the stomach to standardise lumbar position. Using a common palpation procedure, the examiner marked the spine in line with the spinous processes of L1, L3 and L5 bilaterally in line with the inferior angle of the scapula.

The same assessor (the author) examined all subjects in order to reduce the inter-rater variability inherent in these techniques (see (Catley, Tabor et al. 2013). Testing was undertaken separately on left and right sides of the back and the order of testing was randomised, as was the order of levels tested.

3.2.2.1 **Tactile Threshold Discrimination**

Tactile threshold discrimination (TTD) (touch detection) uses Semmes-Weinstein monofilaments (North Coast Medical, Morgan Hill, CA, USA) of varying diameter and stiffness to assess sensory nerve functioning in an area of skin. It is used in a wide variety of contexts, most notably to assess nerve regeneration after injury and in neuropathy (Bell-Krotoski, Weinstein et al. 1993, Weinstein 1993, Rosen 1996). Intra-rater reliability is good to excellent (Novak, Mackinnon et al. 1993, Mawdsley, Behm-Pugh et al. 2004, Collins, Visscher et al. 2010, Auld, Boyd et al. 2011).

3.2.2.2 **Method: Tactile Threshold Discrimination (TTD)**

Semmes-Weinstein monofilaments of varying thickness with corresponding target forces (1.65, 0.008g; 2.83, 0.07g; 3.61, 0.4g; 4.31, 2g; 4.56, 4g; 6.65, 300g) were employed to measure sensory thresholds at L1, L3 and L5 levels. Following a standardised, brief explanation of what the filaments were, each filament was applied perpendicular to the skin with enough force to create a visible bend in the filament. Subjects were instructed to "*say TOUCH every time you feel the filament on your skin*". A standardised protocol for all subjects was carried out beginning with a 1.65, 0.008g filament. Filaments were applied 5 times with a 2 second delay between each repetition. For a positive result, subjects had to report that 3 out of 5 applications elicited a response for each filament. Threshold was established by the method of limits, where stimuli were increased stepwise in filament strength until a response was elicited. The filament with a bending pressure immediately below the established threshold filament was then reapplied to confirm the exact threshold (Yarnitsky 1997).The threshold for each level (L1, L3, L5) was recorded on a standardised body chart.

3.2.2.3 **Two-Point Discrimination**

I have discussed the use of 2PD as an assessment tool in chronic pain in section 3.1.4.

3.2.2.4 **Method: Two-Point Discrimination**

TPD threshold testing followed the principles of the down-up-down method described by Moberg (Moberg 1990) and Seltzer and Seltzer (Seltzer and

Seltzer 1986). A set of electronic digital callipers (Precision Gold®) with a precision of 1mm was lightly applied until the first blanching of the skin. Testing was undertaken bilaterally at each level, and the order of the side of testing was randomised. Based on normative data for TPD threshold (Nolan, 1985), testing was commenced with 70mm between the two points of the callipers. The distance between the points was increased in 5mm increments until the subject was able to perceive only one point instead of two. Each participant was instructed to say 'one' when they felt one point and 'two' when they felt two points. This was confirmed by descending 5mm below this point. An ascending sequence was then applied in 2mm increments until the patient reported two points. Testing continued around these initial values using ascending and descending sequences in 1mm increments until a consistent response was obtained. Catch trials were used to verify that participants were not guessing.

3.2.3 **Data Analysis**

3.2.3.1 **Psychometric And Behavioural Data**

Independent samples t-tests were used to identify differences between MLBP and NuLBP groups with data relating primarily to pain intensity and discrimination (pain on day of scanning numerical rating scale (NRS), SFMPQ). We chose not to assess differences between CLBP subjects and controls with these questionnaires, as our controls were pain-free).

One-way between groups analysis of variance (ANOVA) was used to identify differences between all three groups (controls, MLBP, and NuLBP) in

psychometric questionnaire data (SCL-90-R, EPQ-R, STAI) and pain-related quality of life data (SF-36). Planned comparisons were then used to test the primary hypotheses that CLBP subjects suffer greater psychological distress and poorer quality of life compared to controls and that NuLBP patients suffer greater psychological distress and poorer quality of life compared to MLBP patients. Homogeneity of variance across groups was tested for using Levene's test. Post-hoc and t-tests and planned contrast results were adjusted if homogeneity of variance was violated. All tests were undertaken with a significance level set at p=<0.05.

In the secondary analyses, a Pearson product-moment correlation test was used to investigate relationships between pain and psychometric variables. The relationship strength of the correlation coefficient was determined according to guidelines set out in (Cohen 1988). Significance was set at 0.05 ($p < 0.05$) for all tests.

3.2.3.2 **Clinical Examination Data**

All analyses were completed using SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

One-way analysis of variance testing (ANOVA) was used to examine group differences in 2PD and TTD examination scores. Planned comparisons were then used to test the primary hypothesis that 2PD is disrupted in CLBP participants compared to control subjects, and also in NuLBP compared to MLBP patients. The same planned comparisons were then applied to the TTD data. ANOVAs were also used to examine if there were mean TTD and

2PD differences in different locations of the back and also to see if there were mean TTD and 2PD differences in subjects with differing presentations of back and leg pain, in order to examine whether differences in scores were driven by pain location and/or pain phenotype.

The relationship between 2PD and pain characteristics (pain intensity, pain duration and painDETECT scores) was investigated using Pearson product-moment correlation coefficient. Relationships between TTP and 2PD sensory testing thresholds with pain duration and intensity were explored as both pain intensity and pain duration have been implicated in changes to tactile acuity and cortical representation in chronic pain conditions (Lotze and Moseley 2007). The relationship strength of the correlation coefficient was determined according to guidelines set out in (Cohen 1988). Significance was set at 0.05 ($p < 0.05$) for all tests.

3.3 Subject Demographics

3.3.1 Characterisation By painDETECT

After recruitment patients were classified into MLBP and NULBP subgroups using the painDETECT questionnaire. painDETECT is a highly sensitive, specific and positively predictive accurate questionnaire designed to identify neuropathic components in LBP (Freynhagen 2006). Patients scoring less than 19 were classified as most likely to have mechanical low back pain (MLBP); subjects scoring 19 or more were classified as likely to have a significant neuropathic component to their pain (NuLBP). Based on the

painDETECT questionnaire, 24 NuLBP, 26 MLBP and 20 control subjects completed the study. Mean painDETECT scores for the MLBP group were 9.00, (SD 5.15) and 23.92, (SD 4.36) for the NuLBP group (see Figure 15).

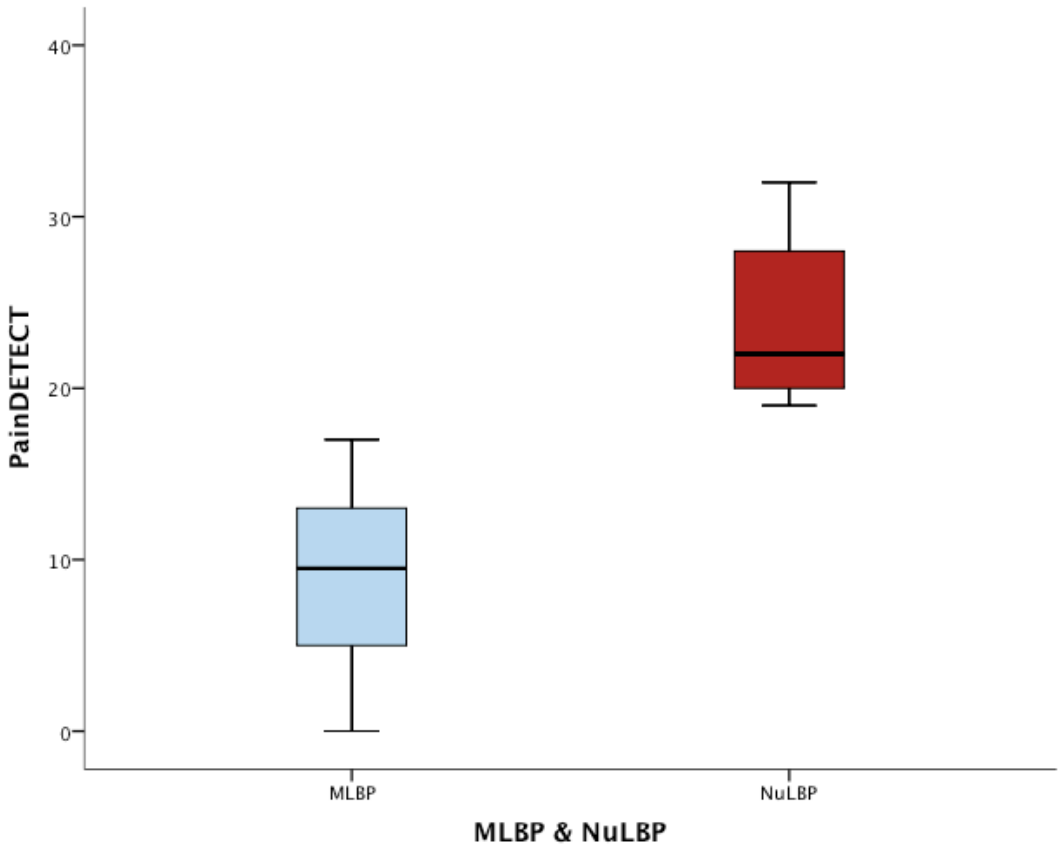

Figure 15: painDETECT scores across groups.

We showed two discrete groups (MLBP M =9.00, SD =5.15; NuLBP M =23.92, SD = 4.36) based on pain phenotype.

1.1.1 There Was No Significant Difference In Age Across Groups.

Table 1: Age and gender across groups.

There was no significant difference in age across groups (ANOVA F (2, 65) = 2.4, p= .102.

	N	M	F	Minimum	Maximum	Mean	Std. deviation
Control	20	9	11	25	59	35.9	9.63
MLBP	26	8	18	21	54	38.15	9.23
NuLBP	24	9	15	25	57	42.71	10.09
Total	70	26	44	-	-	39.07	9.91

Subjects varied from 21-59 years in age. There was no significant difference in age across groups (ANOVA F (2, 65) = 2.4, p= .102) (see Table 1, Figure 16).

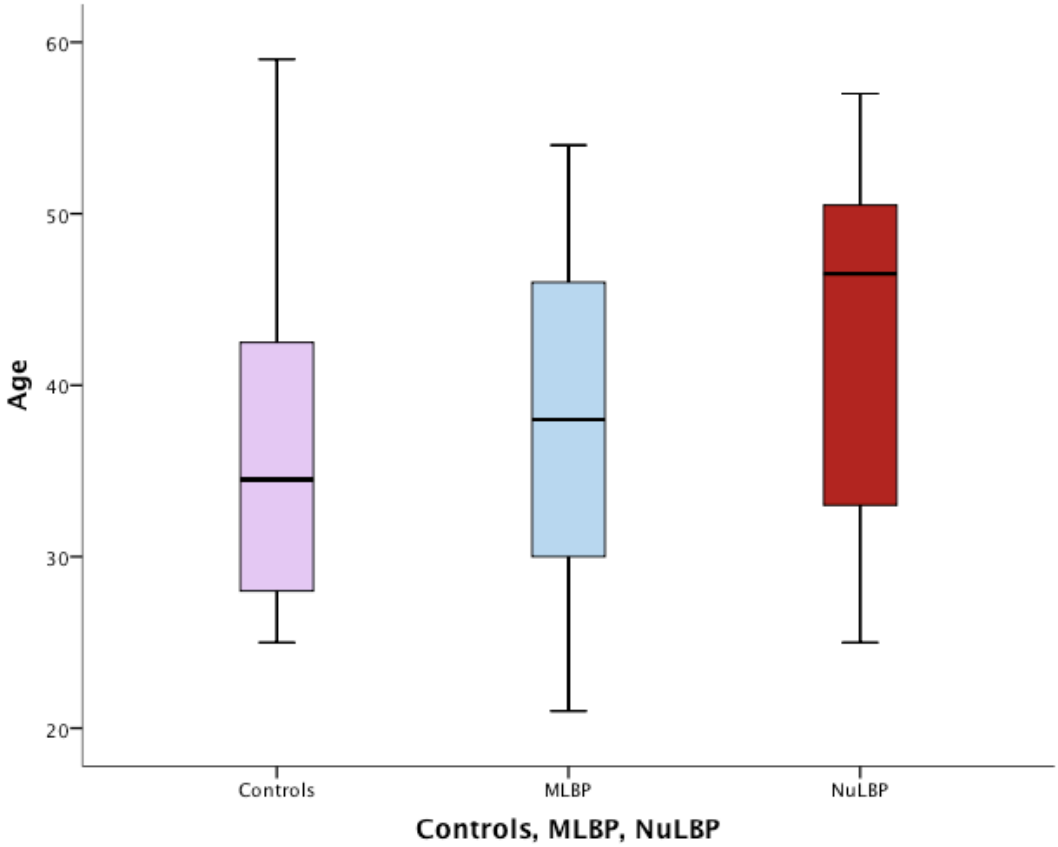

Figure 16:Participant ages by group.

There were no significant differences in age across groups (ANOVA $F(2, 65) = 2.4$, $p = .102$.

1.1.2 There Was No Significant Difference In Duration Of Pain Symptoms Between NuLBP And MLBP.

Table 2: Duration of LBP across groups.

There was no significant difference in duration of pain symptoms for MLBP and NuLBP (t (48)=.150, p = .881).

		N	Mean	Std. Deviation	Minimum	Maximum
Duration (months)	Control	20	-	-	-	-
	MLBP	26	102.15	100.78	12	360
	NuLBP	24	98.25	80.58	12	284

Duration of LBP across subjects varied from 12-360 months. We used an independent samples t-test to compare duration of pain symptoms between groups. There was no significant difference in duration of pain symptoms for MLBP (mean = 102.15, SD = 100.78) and NuLBP (mean = 98.25, SD = 80.58) (t (48) =.150, p = .881) (see Table 2, Figure 17)

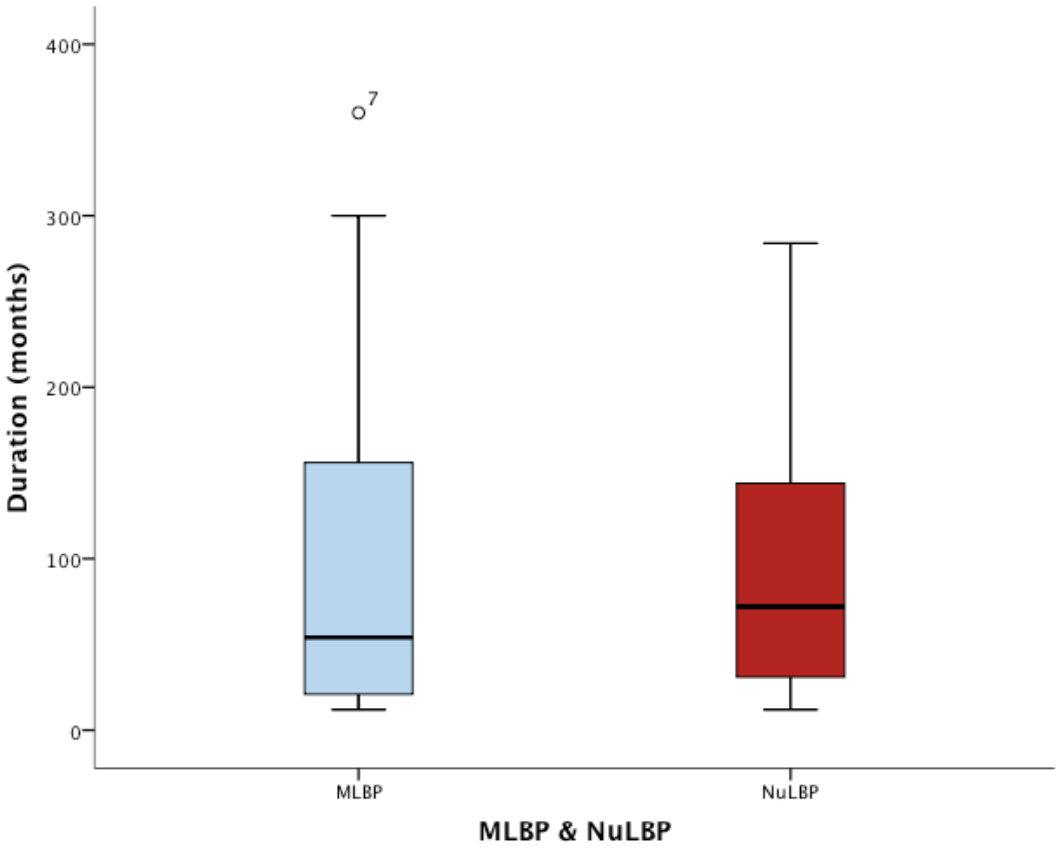

Figure 17: Pain duration MLBP & NuLBP.

Circle represents ID and scores for outliers.

3.4 **Results: Questionnaire Evaluation**

The results of this characterisation chapter encompass all three categories of Melzack's three-dimensional model of pain (1) cognitive-evaluative 2) affective-motivational and 3) sensory-discriminative). I have chosen to discuss the results of the pain-related questionnaires first (NRS, SF-36, SFMPQ), which relate primarily to cognitive evaluation of the sensory and affective components of pain and health-related quality of life. Thereafter, I describe the results of the psychometric questionnaire data (CES-D, SCL-90-R, STAI and EPQ-R), which relate primarily to affective-motivational and

cognitive-evaluative aspects of living with pain. The results of the sensory discrimination tests relate primarily to the sensory-discriminative aspects of the model (however, it may also be argued that processing of sensory discrimination includes significant cognitive-evaluative and affective-motivational components). Importantly, the categories are not mutually exclusive; rather, that to all intents and purposes, they are interdependent.

3.4.1 **Pain-Related Characterisation Across Groups**

3.4.1.1 **NuLBP Patients Demonstrate Significantly Higher Pain On The Day Of Scanning NRS Scores Than MLBP Patients.**

Table 3: Pain intensity on the day of scanning across groups.

		N	Mean	Std. Deviation	Minimum	Maximum
Pain Intensity	Control	20	-	-	-	-
	MLBP	26	4.62	2.06	0	8
	NuLBP	24	6.88	1.70	3	10

An independent samples t-test identified a significant difference in pain scores between the mechanical and neuropathic back pain groups, measured by a numerical rating scale on the day of scanning. Pain ratings were significantly higher ($t(48) = -4.03$, $p=<0.001$) in NuLBP patients (mean= 6.88, SD: 1.70) than in MLBP patients (mean = 4.62, SD: 2.06) (Table 3, Figure 18).

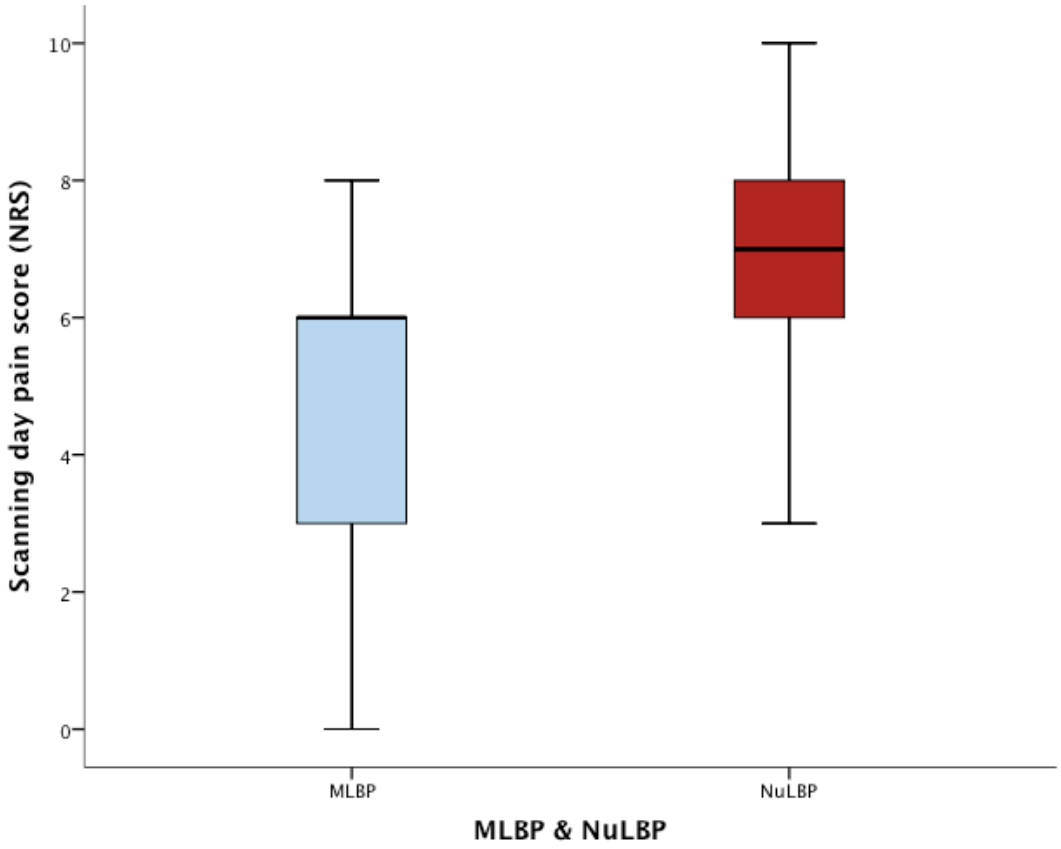

Figure 18: NRS pain on the day of scanning scores across groups.

Significant difference in pain scores identified between the mechanical and neuropathic back pain groups (t (48) = -4.03, p=<0.0001).

3.4.1.2 **Middle And Older Patients Show Significantly Higher Pain NRS Scores Compared To Younger Subjects.**

Table 4: NRS pain intensity on the day of scanning scores across age groups.

Age group	N	Pain intensity	Std. Deviation
20-30	11	4.09	2.34
31-45	18	6	2.22
> 45	21	6.29	1.74
Total	50	5.7	2.20

I used a one-way between subjects analysis of variance (ANOVA) to explore the impact of age on pain intensity, measured by numerical rating scale (NRS) scores on the day of scanning. CLBP patients were grouped into 3 age categories: younger (20-30yrs), middle (31-45yrs) and older (>45yrs). Group means and standard deviations are presented in Table 4.

There was a statistically significant difference in pain NRS scores for the three age groups: $F(2,45) = 4.40$, $p = .018$. Post-hoc comparisons using the Tukey HSD test showed that younger and older groups significantly differed in pain. Younger patients (20-30) demonstrate significantly lower mean pain NRS scores than middle ($p = .05$) or older subjects ($p = .017$). The middle and older subjects did not significantly differ in pain ($p = .902$) (see Figure 19).

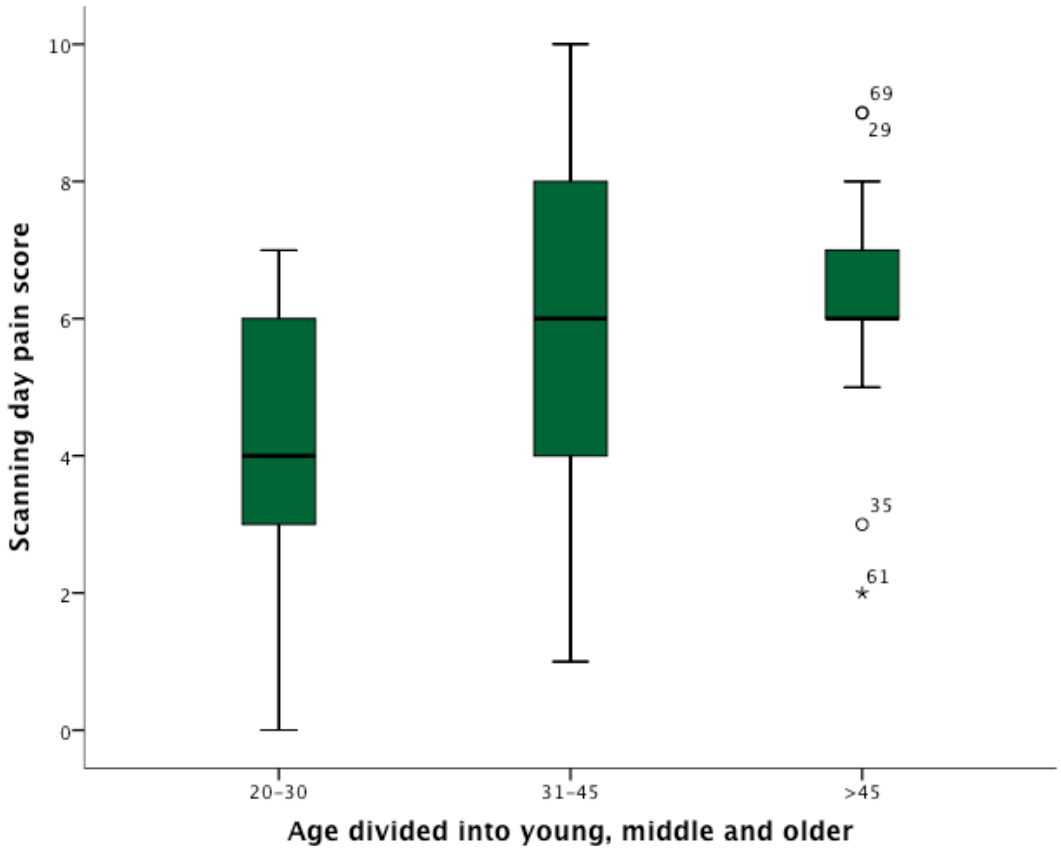

Figure 19: NRS pain intensity on the day of scanning across age groups.

Younger patients (20-30) show significantly lower mean pain NRS scores than middle aged (p = .05) or older subjects (p = .017). Middle and older subjects did not significantly differ in pain (p =.902). Circles represent ID and scores for outliers. Asterisks represent ID and scores for extreme values.

3.4.2 **Short Form Mcgill Pain Questionnaire (SFMPQ)**

3.4.2.1 **NuLBP Patients Show Significantly Higher SFMPQ Visual Analogue Scale (VAS) Pain Scores Than MLBP Patients.**

Table 5: SFMPQ domain scores.

Domain	Group	N	Mean	Std. Deviation
VAS	MLBP	26	61.77	18.89
	NuLBP	22	80.68	12.75
Sensory Pain Descriptors	MLBP	26	10.19	5.87
	NuLBP	22	19.77	7.53
Affective Pain Descriptors	MLBP	20	3.45	2.33
	NuLBP	15	4.93	2.66
Present Pain Intensity	MLBP	26	2.46	0.81
	NuLBP	21	3.71	1.19

Using an independent samples t-test, NuLBP patients demonstrated significantly ($t(46) = 3.99$, $p = < 0.001$) greater VAS pain scores ($M = 80.68$, $SD = 12.75$) than patients with MLBP ($M = 61.77$, $SD = 18.89$) (see Table 5, Figure 20).

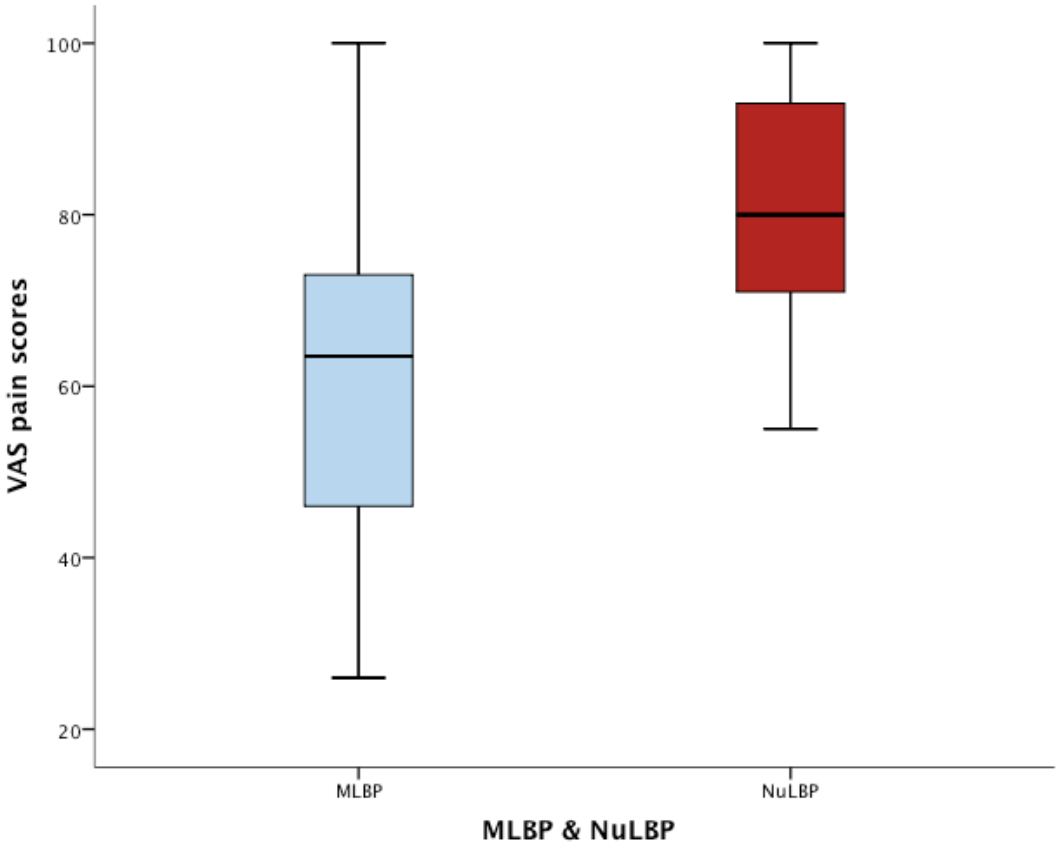

Figure 20: SFMPQ visual analogue scale scores

NuLBP patients had significantly greater VAS pain scores (M = 80.68, SD = 12.75) than patients with MLBP (M = 61.77, SD =18.89); t (46) = 3.99, p = < 0.001).

3.4.2.2 **NuLBP Patients Show Significantly Higher SFMPQ Sensory Pain Scale Descriptor Scores Than MLBP Patients.**

Using an independent samples t-test, NuLBP patients demonstrated significantly greater (t (46) = 4.95, p = < 0.001) SFMPQ Sensory Pain Descriptor Scale scores (M = 19.77, SD = 7.53) than patients with MLBP (M = 10.19, SD = 5.86) (see Table 5, Figure 21).

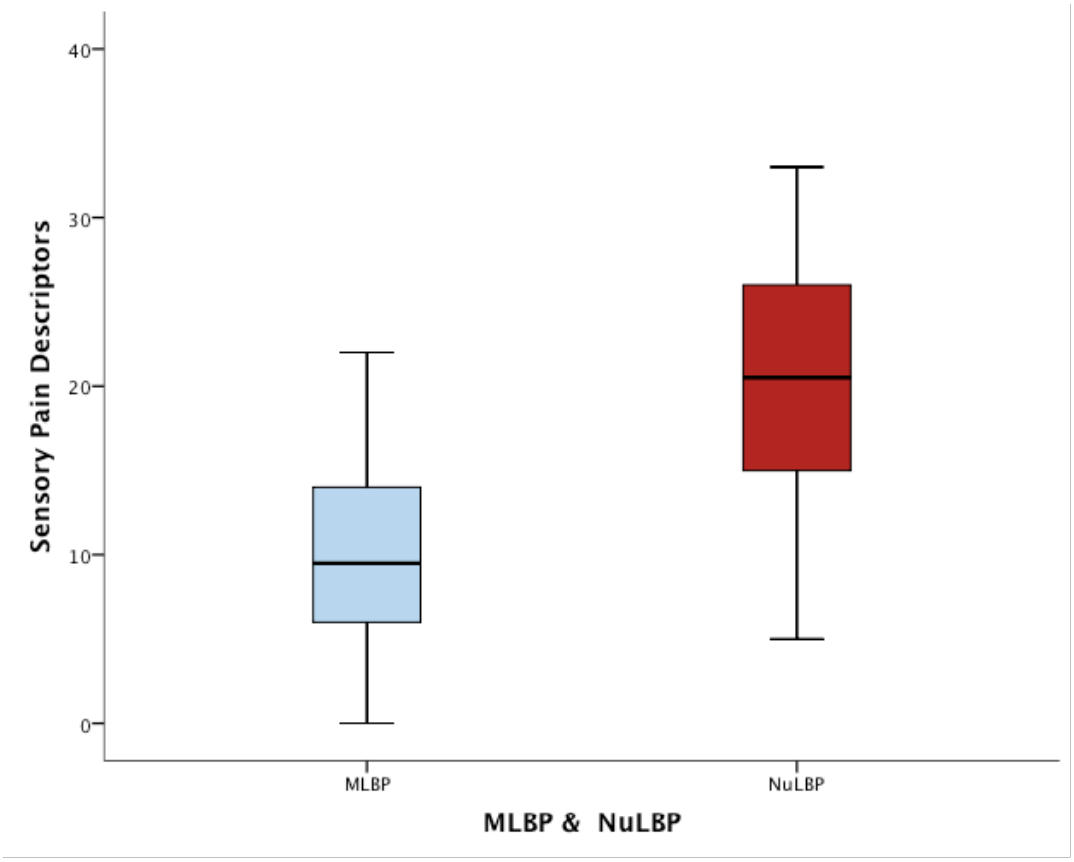

Figure 21: SFMPQ Sensory pain descriptor scores.

NuLBP patients demonstrate significantly greater SFMPQ sensory pain descriptor pain scale scores (M = 19.77, SD = 7.53) than patients with MLBP (M = 10.19, SD =5.86); t (46) = 4.95, p = < 0.001).

3.4.2.3 **NuLBP Patients Show Significantly Higher SFMPQ Present Pain Intensity Scale Scores Than MLBP Patients.**

Using an independent samples t-test, NuLBP patients demonstrated significantly greater SFMPQ Present Pain Intensity scale scores (M = 3.71, SD = 1.19) than patients with MLBP (M = 10.19, SD =5.86); (t (46) = 4.95, p = < 0.001) (Table 5, Figure 22).

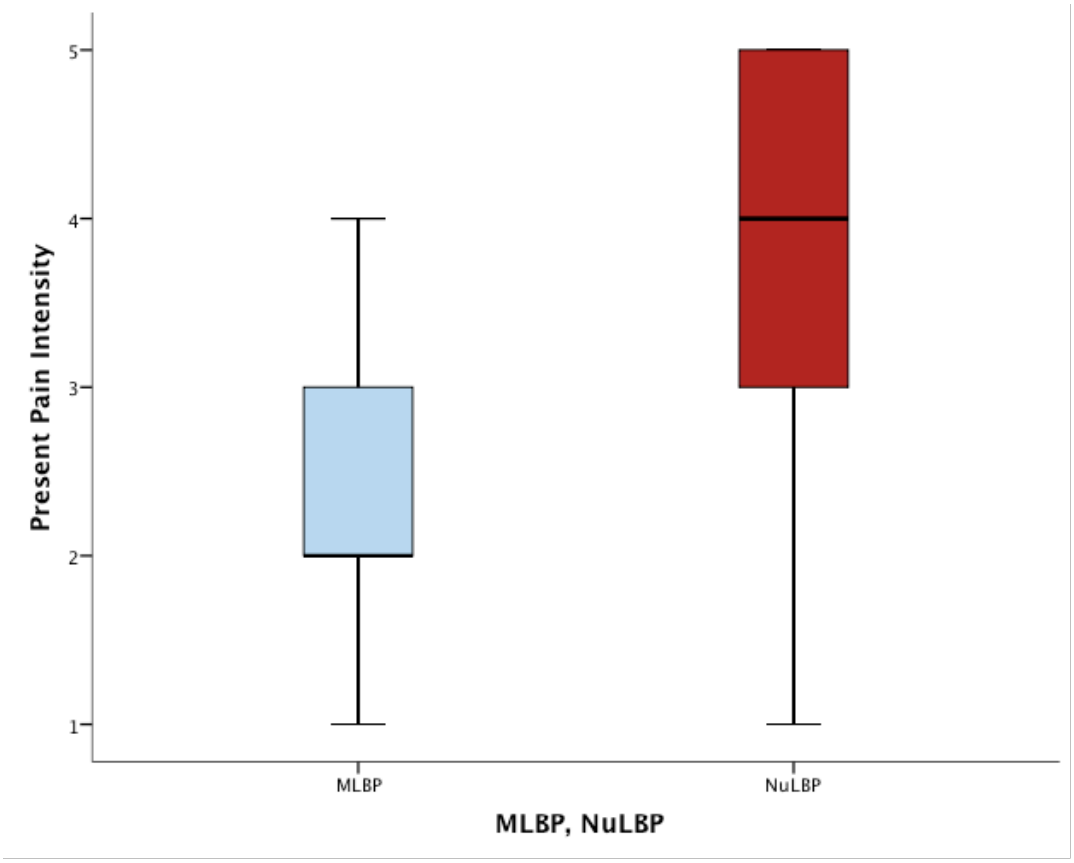

Figure 22: SFMPQ PPI scores across groups.

NuLBP patients demonstrated significantly greater **SFMPQ** Present Pain Intensity scale scores (M = 3.71, SD = 1.19) than patients with MLBP (M = 10.19, SD =5.86); t (46) = 4.95, p = < 0.001).

3.4.2.4 **No Significant Difference Was Seen In SFMPQ Affective Pain Descriptor Scores Between MLBP And NuLBP Groups.**

There was no significant difference in McGill Affective Pain Scores Between MLBP (M =3.45, SD 2.33) And NuLBP Groups (M=4.93, SD=2.66); T (33)= -1.76, P= 0.88). However, Only 35 Scores Were Completed (MLBP N= 20, NuLBP N= 15) **(**Table 5**).**

3.4.3 Rand Medical Outcomes 36-Item Short Form Survey Instrument (SF-36)

3.4.3.1 There Were Significant Differences Between Groups Across All Domains Of The SF-36.

Using one-way analysis of variance (ANOVA), we identified significant differences between groups across all domains of the SF-36 (see Figure 23). See Table 6 for F and significance values and Table 7, Table 8 for mean domain scores).

Table 6: SF-36 ANOVA showing significant differences in all domains.

Domain	df	F	Sig.
Physical Functioning	2, 65	76.78	<0.001
Social Functioning	2, 65	40.21	<0.001
Role-Physical	2, 65	28.93	<0.001
Bodily Pain	2, 65	130.38	<0.001
General Mental health	2, 65	10.95	<0.001
Role-Emotional	2, 65	8.96	<0.001
Vitality	2, 65	20.79	<0.001
General Health Perception	2, 65	21.29	<0.001
Physical Component Summary	2, 65	84.08	<0.001
Mental Component Summary	2, 65	27.98	<0.001

Table 7: RAND Medical Outcomes 36-Item Short Form Survey Instrument (SF-36).

Physical domains: mean values across groups.

Domain	Group	N	Mean	Std. Deviation
Physical Functioning	Control	19	100.00	0.00
	MLBP	26	55.38	20.64
	NuLBP	23	35.43	19.42
Role-Physical	Control	19	100.00	0.00
	MLBP	26	36.54	40.76
	NuLBP	23	26.09	38.05
Bodily Pain	Control	19	98.95	3.15
	MLBP	26	41.54	19.08
	NuLBP	23	24.13	16.95
General Health Perception	Control	19	85.53	10.39
	MLBP	26	52.88	19.86
	NuLBP	23	47.61	25.67
PCS	Control	19	96.12	2.60
	MLBP	26	46.59	19.12
	NuLBP	23	33.32	19.10

Table 8: RAND Medical Outcomes 36-Item Short Form Survey Instrument (SF-36).

Mental domains: mean values across groups.

Domain	Group	N	Mean	Std. Deviation
Vitality	Control	19	73.95	14.20
	MLBP	26	48.08	22.45
	NuLBP	23	36.30	18.48
Social Functioning	Control	19	96.71	11.67
	MLBP	26	65.38	23.53
	NuLBP	23	42.93	19.15
Role-Emotional	Control	19	94.74	12.49
	MLBP	26	70.51	40.36
	NuLBP	23	47.83	42.43
General Mental health	Control	19	81.68	10.27
	MLBP	26	71.23	16.93
	NuLBP	23	58.96	17.94
MCS	Control	19	86.77	7.51
	MLBP	26	63.80	21.10
	NuLBP	23	46.51	18.41

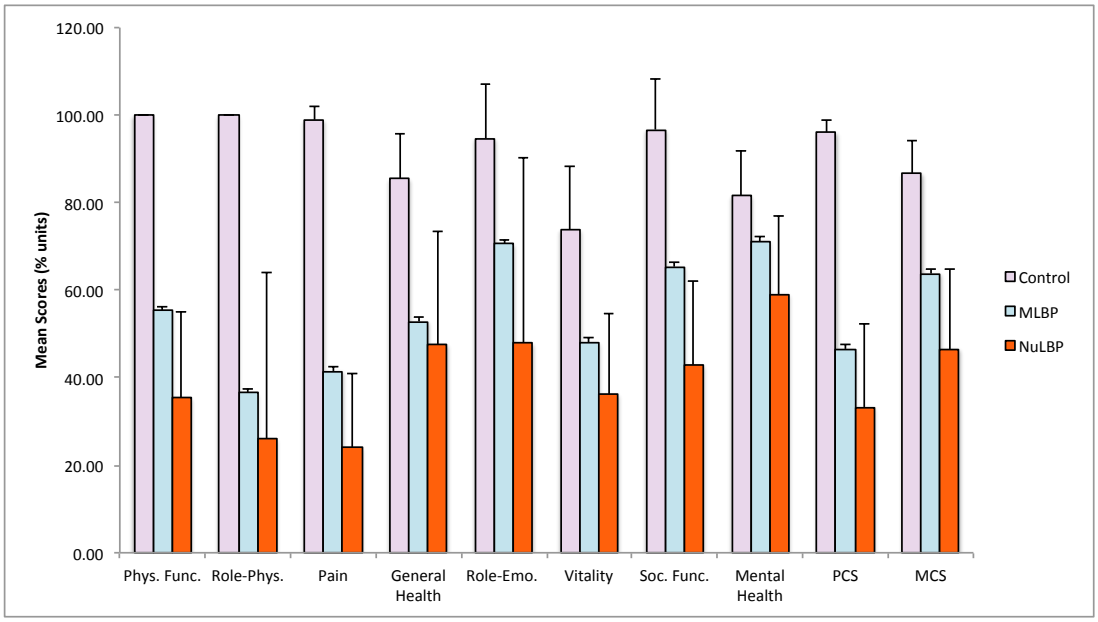

Figure 23: SF-36: Mean scores across groups.

Scores are expressed a percentages. Error bars show 1 standard deviation. One way analysis of variance (ANOVA) shows significant differences between subject groups in all SF-36 domains (physical functioning F (2,65) = 76.78, p = <0.001; Role-physical F (2,65) = 28.93, p = <0.001; Bodily pain F (2,65) = 130.38, p = <0.001; General Health perception F (2,65) = 21.29, p = <0.001; Role-emotional F (2,65) = 8.96, p = <0.001; Vitality F (2,65) = 20.79, p = <0.001; Social functioning F (2,65) = 40.21, p = <0.001; General Mental Health F (2,65) = 10.95, p = <0.001; Physical component summary F (2,65) = 84.08, p = <0.001; Mental component summary F (2,65) = 27.98, p = <0.001

3.4.3.2 **CLBP Patients Experience Significantly Poorer Physical And Mental Health Related Quality Of Life Across All Domains Of The SF-36 Compared To Controls.**

Using ANOVA planned comparisons; we observed reduced scores (indicating poorer physical and mental health related quality of life) in CLBP patients compared to controls in *all* SF-36 domains (see Figure 23). Mean scores are listed in Table 7,Table 8; degrees of freedom, t and significance values are listed in Table 9.

Table 9: SF-36 ANOVA planned comparisons: CLBP compared to controls.

Domain	t value	df	Sig. value
Physical Functioning	19.07	46.81	<0.001
Role-Physical	12.20	46.85	<0.001
Bodily Pain	24.73	53.84	<0.001
General Health Perception	8.65	58.88	<0.001
PCS	20.07	50.49	<0.001
Vitality	6.15	65.00	<0.001
Social Functioning	10.48	57.66	<0.001
Role-Emotional	5.40	60.94	<0.001
General Mental health	4.83	54.19	<0.001
MCS	9.56	64.98	<0.001

3.4.3.3 **NuLBP Patients Experience Significantly Poorer Physical And Mental Health Related Quality Of Life Across Several Domains Of The SF-36 Compared To MLBP Patients.**

Using ANOVA planned comparisons, we observed reduced scores (indicating poorer physical and mental health related quality of life) in NuLBP patients compared to MLBP in the following SF-36 physical domains: physical functioning, bodily pain and physical component summary (see Figure 23). Mean scores are listed in Table 7; degrees of freedom, t and significance values are listed in Table 10.

We also saw reduced scores in NuLBP patients compared to MLBP in the following SF-36 mental domains: Vitality, social functioning, general mental health and mental component summary. Mean scores are listed in Table 8; degrees of freedom, t and significance values are listed in Table 10.

Table 10: SF-36 ANOVA planned comparisons: NuLBP compared to MLBP.

Domains with significant p values at <0.05.

Domain	t value	df	Sig. value
Physical Functioning	3.49	46.81	0.001
Bodily Pain	3.38	47.00	0.001
PCS	2.43	46.28	0.019
Vitality	2.15	65.00	0.035
Social Functioning	3.68	46.70	0.001
General Mental health	2.45	45.48	0.018
MCS	3.06	46.99	0.004

3.4.3.4 **No Statistically Significant Difference In SF-36 Scores Were Identified Between Mechanical And Neuropathic Back Pain Groups In The Following Domains.**

Using ANOVA planned comparisons, we did not observe statistically significant differences between NuLBP and MLBP groups in the following SF-36 domains: Role-Physical (limitations in usual role activities because of physical health problems), General Health (general health perceptions) and Role-Emotional (limitations in usual role activities because of emotional problems) (see Figure 23). Mean scores are listed in Table 7, Table 8; degrees of freedom, t and significance values are listed in Table 11.

Table 11: SF-36 ANOVA planned comparisons: NuLBP compared to MLBP

Domains with non-significant p values at <0.05 .

Domain	t value	df	Sig. value
Role-Physical	0.93	46.85	0.358
General Health Perception	0.80	41.28	0.43
Role-Emotional	1.91	45.60	0.062

3.4.4 Group Psychometric Evaluation

3.4.5 Revised Symptom Checklist 90 Questionnaire (SCL-90-R).

Table 12: SCL-90-R Group mean values.

Domain	Group	N	Mean	Std. Deviation
Somatisation	Control	19	42.68	9.10
	MLBP	26	62.69	9.12
	NuLBP	24	69.58	9.38
Obsessive-Compulsive	Control	19	50	10.29
	MLBP	26	59.77	10.45
	NuLBP	24	65.21	9.97
Interpersonal Sensitivity	Control	19	46.63	6.33
	MLBP	26	53.12	12.43
	NuLBP	24	61.38	12.36
Depression	Control	19	47.32	10.61
	MLBP	26	56.92	11.29
	NuLBP	23	62.48	12.91
Anxiety	Control	19	42.53	8.26
	MLBP	26	51.85	11.98
	NuLBP	24	60.46	14.23
Hostility	Control	19	44.79	7.42
	MLBP	26	53.27	11.33
	NuLBP	24	55.38	13.86

Table 13: SCL-90-R Group mean values.

Domain	Group	N	Mean	Std. Deviation
Phobic Anxiety	Control	19	46.89	7.98
	MLBP	26	50.54	11.17
	NuLBP	24	58.96	13.08
Paranoid Ideation	Control	19	46.21	7.71
	MLBP	26	49.62	10.23
	NuLBP	24	54.04	15.00
Psychoticism	Control	19	45.63	4.55
	MLBP	26	55.85	11.38
	NuLBP	24	62.25	13.39
Global Severity Index	Control	19	43.84	11.21
	MLBP	26	58.27	9.99
	NuLBP	24	65.17	10.45
Positive Symptom Total	Control	19	43.89	9.36
	MLBP	26	54.85	10.02
	NuLBP	23	63.26	8.97
Positive Symptom Distress Index	Control	19	46.58	8.58
	MLBP	26	61.31	9.95
	NuLBP	24	62.42	10.48

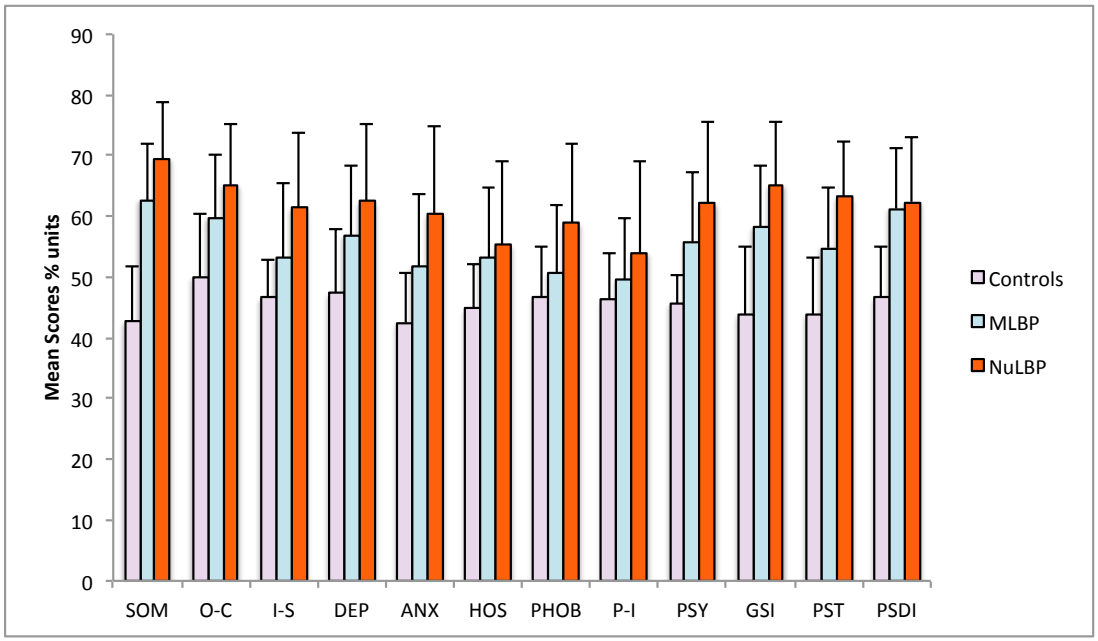

Figure 24: Mean SCL-90-R scores across groups.

Scores are expressed a percentages. Error bars show 1 standard deviation. One way analysis of variance (ANOVA) shows significant differences between subject groups in all SCL-90-R domains except paranoid ideation (Somatisation F (2,66) = 47.61, p = <0.001; Obsessive-Compulsive F (2,66) = 11.82, p=<0.001; Depression F (2,65) =9.60, p = <0.001; Interpersonal Sensitivity F(2,66) =8.86, p=<0.001; Anxiety F 2,66 = 11.91, p = <0.001; Hostility F (2,66) = 4.96, p=0.01; Psychoticism F (2,66) = 12.56, p = <0.0001; Global Severity Index F (2,66) = 22.35, p = <0.0001; Positive Symptom Total F (2,65) = 21.67, p=<0.0001 and the Positive Symptom Distress Index F (2,66) = 16.82 p=<0.0001).

3.4.5.1 **There Were Significant Differences Between Subject Groups In All SCL-90-R Domains Except Paranoid Ideation.**

We used one–way analysis of variance (ANOVA) to identify differences between subject groups. We observed significant differences between subject groups in all SCL-90-R domains except Paranoid Ideation (see Figure 24). Mean scores are listed in Table 12, Table 13; F and significance values are listed in Table 14.

Table 14: SCL-90-R ANOVA, F and significance values.

Domain	F value	Sig. value
Somatisation	F (2,66) = 47.61	p = <0.001
Obsessive-Compulsive	F (2, 66) = 11.82	p = <0.001
Depression	F (2,65) = 9.60	p = <0.001
Interpersonal Sensitivity	F (2,66) = 8.86	p = <0.001
Anxiety	F (2,66) =11.91	p = <0.001
Hostility	F (2,66) = 4.96	p = 0.01
Phobic Anxiety	F (2,66) = 6.83	p = 0.002
Psychoticism	F (2,66) =12.56	p = <0.001
Global Severity Index	F (2,66) = 22.35	p = <0.001
Positive Symptom Distress Index	F (2,66) = 16.82	p = <0.001
Positive Symptom Total	F (2,65) = 21.67	p = <0.001
Paranoid Ideation	F (2,66) = 2.48	p = 0.092

3.4.5.2 **CLBP Patients Show Greater Psychological Distress Compared To Controls In All SCL-90-R Domains.**

Using ANOVA planned comparisons; we observed increased scores (indicating greater psychological distress) in CLBP patients compared to

controls in *all* SCL-90-R domains (see Figure 24). Mean scores are listed in (see Table 12 and Table 13); degrees of freedom, t and significance values are listed in Table 15.

Table 15: SCL-90-R ANOVA, planned comparisons CLBP compared to controls, t and significance values.

Domain	t value	df	Sig. value
Somatisation	9.45	66	p = <0.001
Obsessive-Compulsive	4.52	66	p = <0.001
Interpersonal Sensitivity	4.66	60.39	p = <0.001
Depression	3.92	65	p = <0.001
Anxiety	5.12	50.86	p = 0.013
Hostility	3.85	53.63	p = <0.001
Phobic anxiety	3.12	48.95	p = 0.03
Psychoticism	6.55	63.15	p = 0.001
Paranoid ideation	2.21	50.97	p = 0.032
Global Severity Index	6.32	66	p = <0.001
Positive Symptom Total	5.91	65	p = <0.001
Positive Symptom Distress Index	5.79	66	p = <0.001

3.4.5.3 **NuLBP Patients Show Greater Psychological Distress Compared To MLBP Patients In Several SCL-90-R Domains.**

Using ANOVA planned comparisons; we observed increased scores (indicating greater psychological distress) in NuLBP patients compared to MLBP patients in several SCL-90-R domains (see Figure 24). Mean scores are listed in (see Table 12 and Table 13); t and significance values are listed in (see Table 16).

Table 16: SCL-90-R ANOVA: planned comparisons NuLBP compared to MLBP, t and significance values

Domain	t value	df	Sig. value
Somatisation	2.65	66	p = 0.01
Interpersonal Sensitivity	2.35	47.72	p = 0.023
Anxiety	2.31	45.17	p = 0.026
Psychoticism	6.55	45.35	p = <0.001
Phobic anxiety	2.44	45.45	p = 0.019
Global Severity Index	2.32	66	p = 0.023
Positive Symptom Total	3.1	65	p = 0.003

3.4.6 **CES-D**

3.4.6.1 **There Were Significant Differences Between Subject Groups In CES-D Scores.**

Using one–way analysis of variance (ANOVA), we were able to identify significant differences between subject groups in CES-D scores, F (2,67) = 27.12, p = <0.001 (see Table 17 and Figure 26).

Table 17: CES-D scores across groups.

Group	N	Mean	Std. Deviation
Control	20	4.55	5.69
MLBP	26	11.42	8.37
NuLBP	24	23.33	10.67

3.4.6.2 CLBP Subjects Report Significantly Greater Depressive Symptoms Than Controls.

Using ANOVA planned comparisons, we observed that CLBP patients reported significantly greater depressive symptoms compared to controls, t (55.70) = 6.88, p = <0.001 (see Table 17, Figure 25).

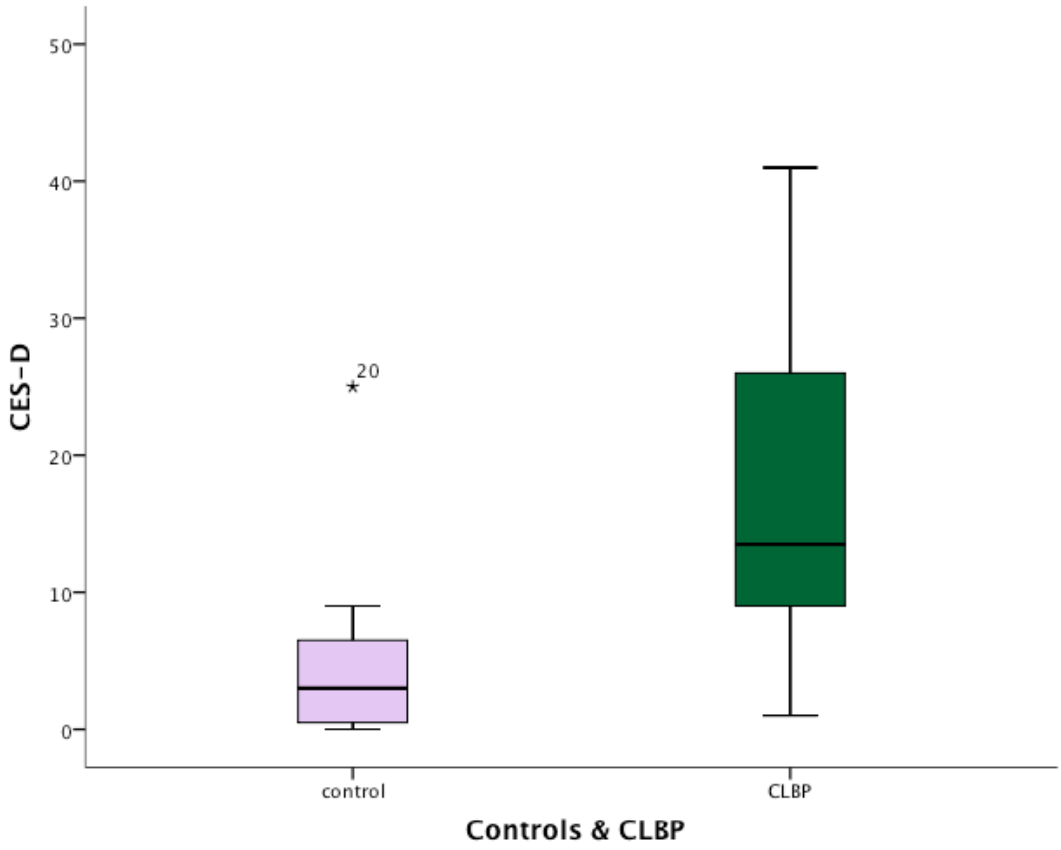

Figure 25: CES-D scores: ANOVA planned comparisons, CLBP compared to controls.

CLBP patients report significantly greater depressive symptoms compared to controls, *t* (55.70) = 6.88, p = <0.001. Asterisks represent ID and scores for extreme values.

3.4.6.3 **NuLBP Subjects Report Significantly Greater Depressive Symptoms Than MLBP Subjects.**

Using ANOVA planned comparisons, we observed that NuLBP patients reported significantly greater depressive symptoms compared to MLBP subjects, t (55.70) = 6.88, p = <0.001 (see Table 17, Figure 26)

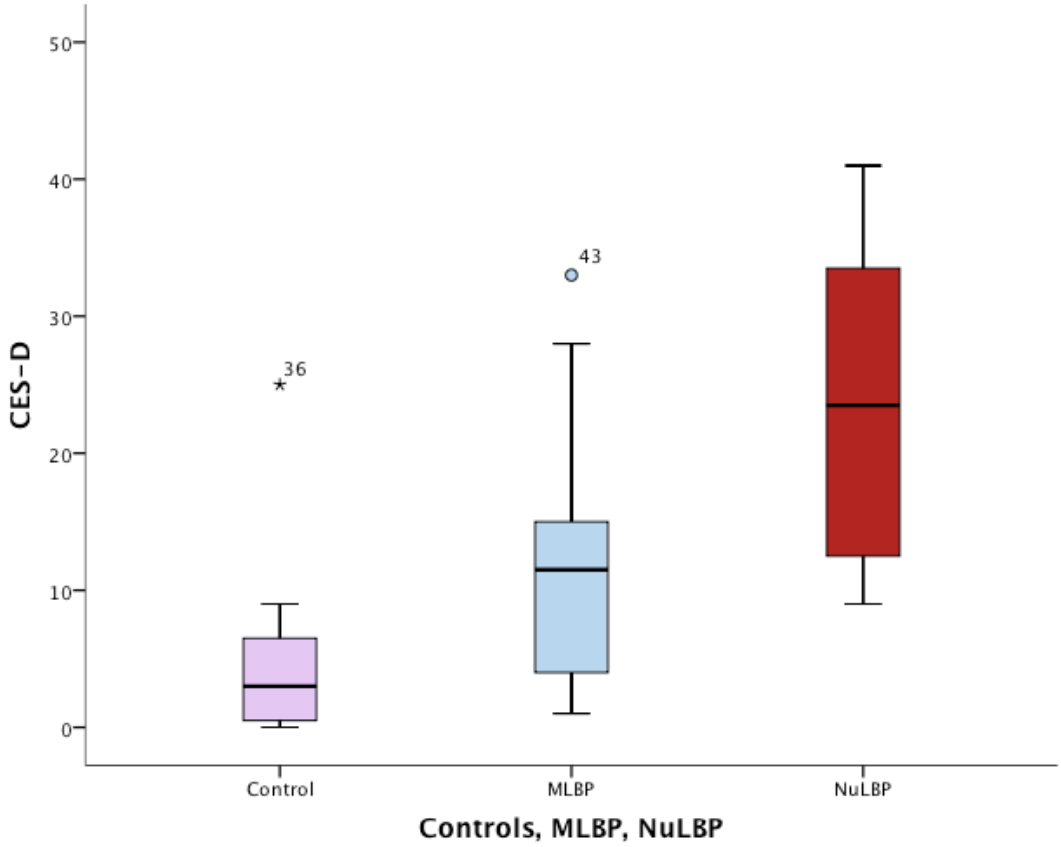

Figure 26: Mean CES-D scores across groups.

There are significant differences between subject groups in CES-D scores, *F* (2,67) = 27.12, *p* = <0.001. CLBP patients report significantly greater depressive symptoms compared to controls, *t* (55.70) = 6.88, p = <0.001. NuLBP patients report significantly greater depressive symptoms compared to MLBP subjects, *t* (55.70) = 6.88, p = <0.001. Circles represent ID and scores for outliers. Asterisks represent ID and scores for extreme values.

3.4.7 **STAI State And Trait Anxiety**

3.4.7.1 **There Were Significant Differences Between Subject Groups In STAI State Scores And STAI Trait Scores.**

Using one–way analysis of variance (ANOVA), we were able to identify significant differences between subject groups in STAI state scores, $F(2,66) = 9.02$, $p = <0.001$ and STAI trait scores, $F(2,67) = 10.77$, $p = <0.001$ (see Table 18 and Figure 27).

Table 18: Mean STAI state and trait scores across groups.

Domain	Group	N	Mean	Std. Deviation
STAI State	Control	19	29.53	9.65
	MLBP	26	36.42	8.02
	NuLBP	24	43.83	14.34
STAI Trait	Control	20	32.8	8.08
	MLBP	26	42.31	10.13
	NuLBP	24	46.63	11.18

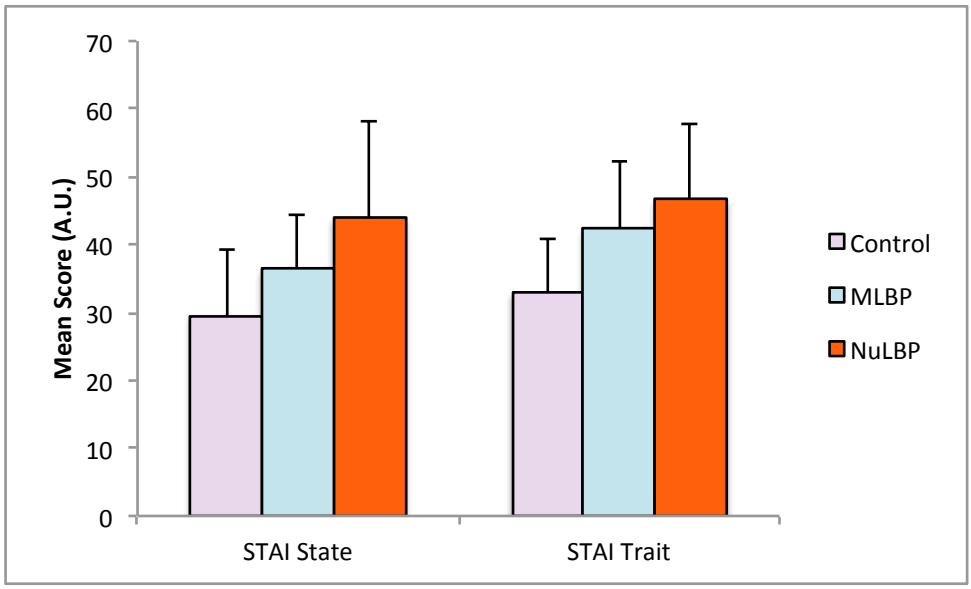

Figure 27: Mean STAI state and trait scores across groups.

Scores are expressed as arbitrary units. Error bars show 1 standard deviation. One-way analysis of variance (ANOVA) shows significant differences between subject groups in STAI state scores ($F(2,66) = 9.02$, $p = <0.001$) and STAI trait scores ($F(2,67) = 10.77$, $p = <0.001$).

3.4.7.2 **STAI State Scores Are Greater In CLBP Patients Than Controls.**

Using planned comparisons, we observed greater state anxiety in CLBP patients compared to controls (t (37.88) = 3.83, p = <0.001) (Table 18, Figure 28).

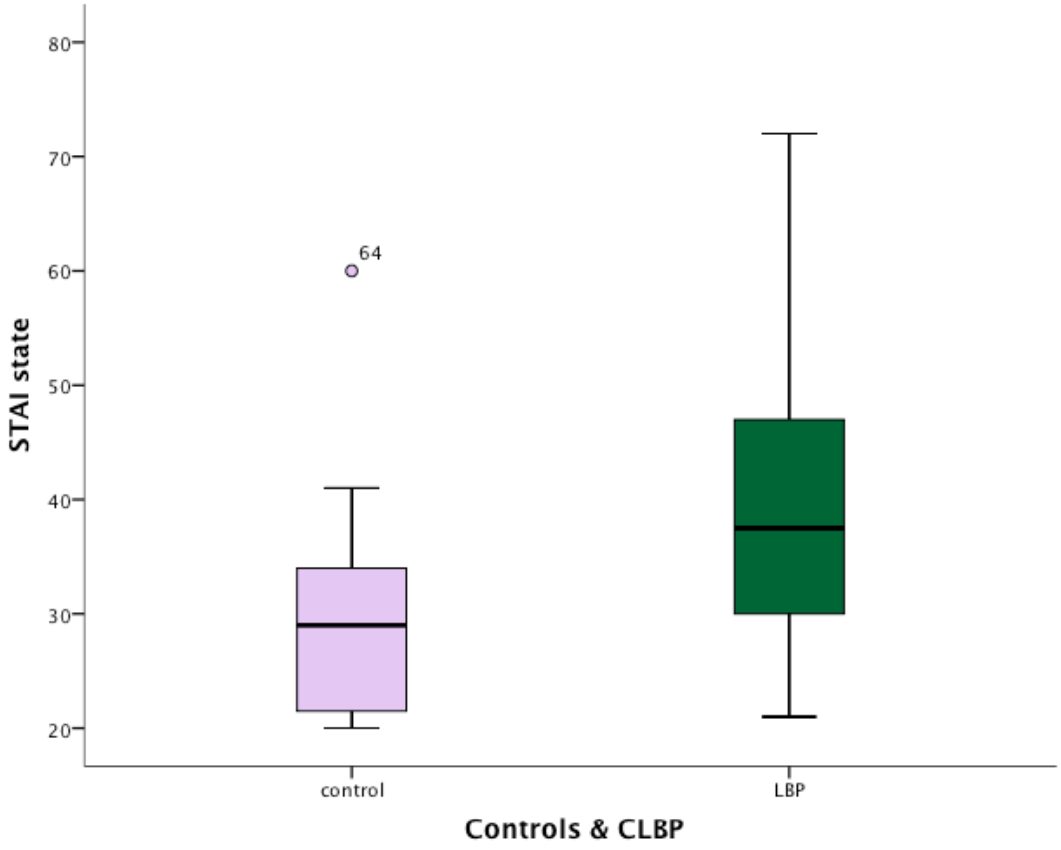

Figure 28: Mean STAI state scores.

CLBP patients report greater state anxiety compared to controls (t (37.88) = 3.83, p = <0.001). Circles represent ID and scores for outliers.

3.4.7.3 **STAI Trait Anxiety Scores Are Greater In CLBP Patients Than Controls.**

Using planned comparisons, we observed greater trait anxiety in CLBP patients compared to controls (t (67) = 4.42, p = <0.001) (Table 18, Figure 29).

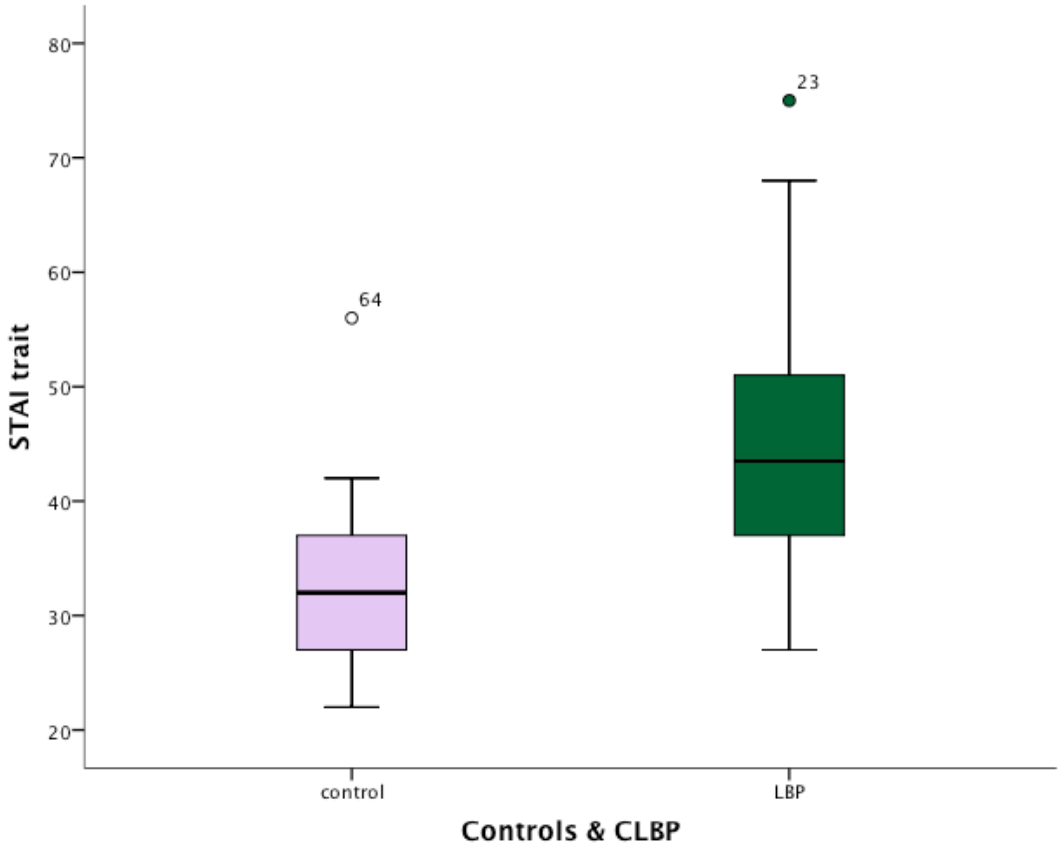

Figure 29: Mean STAI trait scores.

CLBP patients report greater trait anxiety in CLBP patients compared to controls (t (67) = 4.42, p = <0.001). Circles represent ID and scores for outliers

3.4.7.4 **NuLBP Subjects Report Greater STAI State Anxiety Scores Compared To MLBP Subjects.**

Using planned comparisons, we observed greater STAI state anxiety scores in NuLBP patients compared to MLBP patients (t (35.49) = 2.23, p = 0.032) (Table 18, Figure 30).

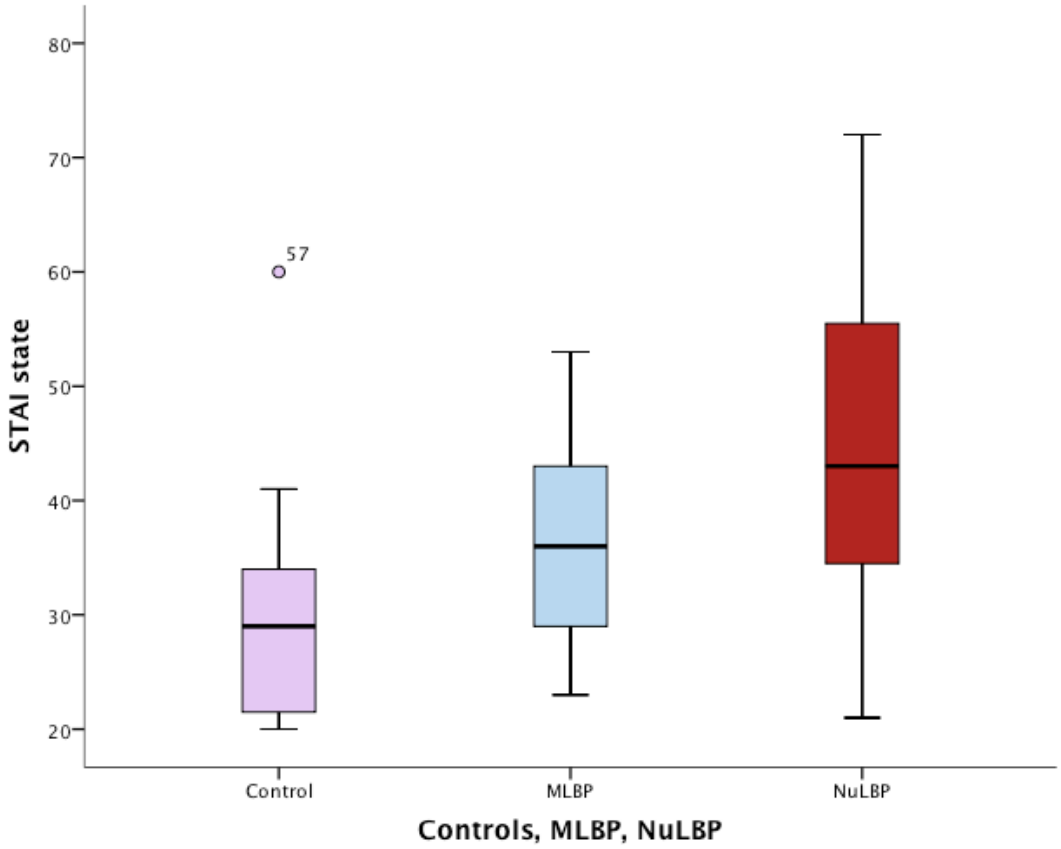

Figure 30: Mean STAI state scores across groups.

NuLBP subjects report greater STAI state anxiety scores compared to MLBP patients. (t (35.49) = 2.23, p = 0.032). Circles represent ID and scores for outliers.

There were no significant differences between NuLBP patients and MLBP patients in STAI trait scores, t (67) = 1.53, p = 0.131, (Table 18, Figure 31).

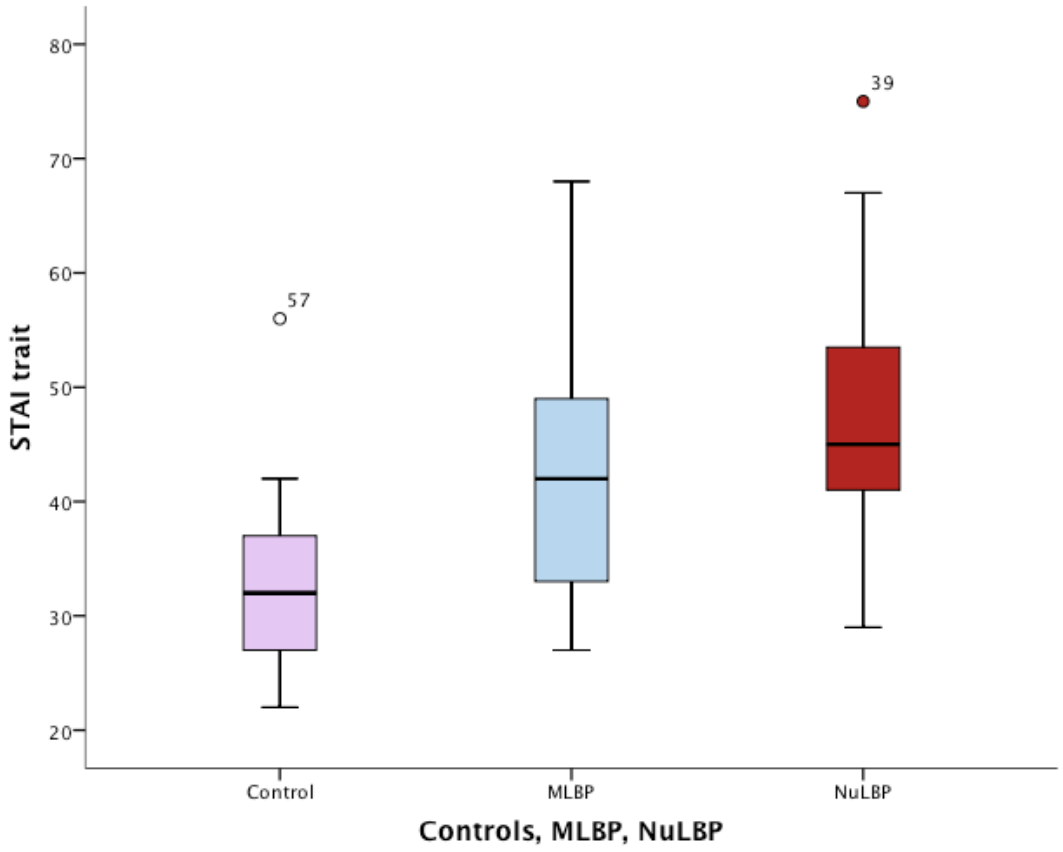

Figure 31: Mean STAI trait scores across groups.

There are no significant differences between NuLBP patients and MLBP patients (t (67) = 1.53, p = 0.131). Circles represent ID and scores for outliers.

3.4.8 **EPQ-R**

3.4.8.1 **There Were Significant Differences Between Subject Groups In EPQ-R-P Scores.**

Significant group differences in EPQ-R-P (psychoticism) scores were identified using one-way analysis of variance (ANOVA), F (2,66) = 3.79, p = 0.028. There were no statistically significant differences between groups on EPQ-R-E, F (2,66) = 2.62, p = 0.081 and EPQ-R-N, F (2,66) = 2.09, p = 0.131 scales (see Table 19 and Figure 32).

Table 19: EPQ-R scores across groups.

Domain	Group	N	Mean	Std. Deviation
EPQ-R-E	Control	20	15.2	3.85
	MLBP	26	11.96	5.11
	NuLBP	23	13	5.17
EPQ-R-N	Control	20	8.4	5.37
	MLBP	26	10.19	5.61
	NuLBP	23	12	6.23
EPQ-R-P	Control	20	3.8	2.73
	MLBP	26	4.46	2.53
	NuLBP	23	6.13	3.39

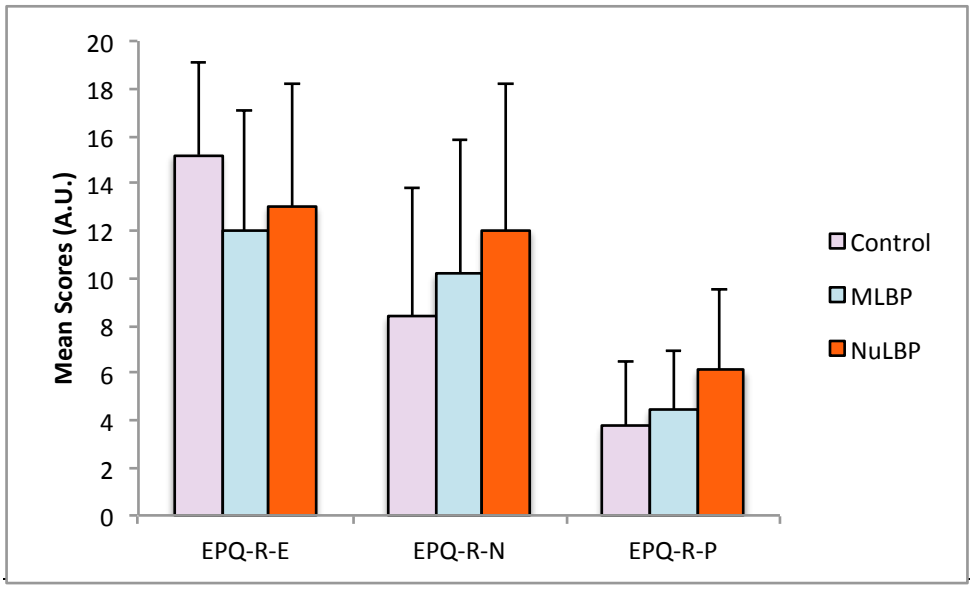

Figure 32: Mean EPQ-R scores across groups.

Scores are expressed as arbritrary units. Error bars show 1 standard deviation. One-way analysis of variance (ANOVA) shows significant differences between subject groups in in EPQ-R-P (psychoticism) scores ($F(2,66) = 3.79$, $p = 0.028$) but not in EPQ-R-E (extraversion) ($F(2,66) = 2.62$, $p = 0.081$) and EPQ-R-N (neuroticism) ($F(2,66) = 2.09$, $p = 0.131$) scores.

3.4.8.2 **EPQ-R-E Scores Are Greater In Controls Than CLBP Patients.**

Using planned comparisons, we observed greater EPQ-R-E scores in controls compared to CLBP patients, $t(66) = 2.13$, $p = 0.037$, indicating that CLBP patients display fewer characteristics associated with extraversion, such as sociability, out-goingness and impulsivity (see Table 19).

3.4.8.3 **EPQ-R-P scores are greater in NuLBP compared to MLBP subjects**

Using planned comparisons, we observed greater EPQ-R-P scores in NuLBP patients compared to MLBP, $t(66) = 2.01$, $p = 0.048$, indicating greater characteristics associated with psychoticism (aggressiveness, coldness, anti-social, tough mindedness). CLBP patients, as a whole, also

scored greater compared to controls on the EPQ-R-P scale but this narrowly missed statistical significance, t (66) = 1.94, p = 0.056 (see Table 19).

3.4.9 **PainDETECT Correlations**

The relationship between painDETECT scores and other variables were investigated using Pearson product-moment correlation coefficient.

Table 20: painDETECT correlations with pain intensity, pain duration and CES-D scores.

	painDETECT	pain intensity	pain duration	CES-D
Pearson Correlation	1	.636**	0.079	.592**
Sig. (2-tailed)		<0.001	0.588	<0.001
N	50	50	50	50

** Correlation is significant at the 0.01 level (2-tailed).

3.4.9.1 **There Was A Strong, Significant Correlation Between PainDETECT And Pain Intensity.**

There was a strong, significant correlation between painDETECT and pain intensity, measured by NRS, on the day of scanning (see Table 20 for r and significance values).

3.4.9.2 **There Was A Strong, Significant Correlation Between PainDETECT And CES-D Scores.**

There was a strong, significant correlation between painDETECT and CES-D scores (see Table 20 for r and significance values).

There was no significant relationship between painDETECT and pain duration (see Table 20 for r and significance values).

3.4.9.3 **PainDETECT And SF-36**

Table 21: painDETECT and SF-36 correlations.

There are strong to moderate, signifiicant correlations with all domains of the SF-36.

	PainDETECT	Physical Function	Social Function	Role-Physical	Bodily Pain	Mental Health	Role-Emotional	Vitality	General Health Perception	PCS	MCS
Pearson Correlation	1	-.555**	-.490**	-0.132	-.463**	-.417**	-.402**	-.427**	-.377**	-.441**	-.530**
Sig. (2-tailed)		<0.001	<0.001	0.367	0.001	0.003	0.004	0.002	0.008	0.002	<0.001
N	50	49	49	49	49	49	49	49	49	49	49

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.9.4 **There Were Strong, Significant Correlations Between PainDETECT And Physical Functioning And Mental Component Summary SF-36 Domains.**

There were strong, significant correlations between painDETECT and the SF-36 domains of Physical Functioning and Mental Component Summary (see Table 21 for r and significance values).

3.4.9.5 **There Were Moderate, Significant Correlations Between PainDETECT And The Following SF-36 Domains.**

There were moderate, significant correlations between painDETECT and the following SF-36 domains: Social Functioning, Bodily Pain, Role-Emotional, Mental Health, Vitality, General Health perception and the Physical Component Summary (see Table 21 for r and significance values).

3.4.9.6 **PainDETECT And SFMPQ**

Table 22: painDETECT and SFMPQ correlations.

	PainDETECT	Sensory Pain Descriptors	Affective Pain Descriptors	VAS	Present Pain Intensity
Pearson Correlation	1	.623**	.490**	.552**	.493**
Sig. (2-tailed)		<0.001	0.003	<0.001	<0.001
N	50	48	35	48	47

** Correlation is significant at the 0.01 level (2-tailed).

3.4.9.7 **There Was A Strong, Significant Correlation Between PainDETECT And The SFMPQ Sensory Pain Descriptor Scale And SFMPQ Visual Analogue Scale (VAS).**

There was a strong, significant correlation between painDETECT and the SFMPQ sensory pain descriptor scale and SFMPQ VAS (see Table 22 for r and significance values).

3.4.9.8 **There Were Moderate, Significant Correlations Between PainDETECT And SFMPQ Affective Pain Scale Scores And SFMPQ Present Pain Intensity Scale Scores.**

There were moderate, significant correlations between painDETECT and SFMPQ affective pain scale scores and SFMPQ present pain intensity scale scores (see Table 22 for r and significance values).

3.4.9.9 **PainDETECT And SCL-90-R**

Table 23: painDETECT and SCL-90-R correlations.

There was a strong, significant correlation with the SCL-90-R Somatisation scale and moderate, significant correlations with Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Phobic-Anxiety, Paranoid Ideation, Psychoticism, Positive Symptom Total and Global Severity Index scales

	PainDETECT	Somatisation	Obsessive-Compulsive	Interpersonal Sensitivity	Depression	Anxiety	Hostility	Phobic Anxiety	Paranoid Ideation	Psychoticism	Global Severity Index	Positive Symptom Total	Positive Symptom Distress Index
Pearson Correlation	1	.512**	.404**	.420**	.334*	.379**	0.255	.416**	.290*	.416**	.456**	.487**	0.177
Sig. (2-tailed)		<0.001	0.004	0.002	0.019	0.007	0.073	0.003	0.041	0.003	0.001	<0.001	0.22
N	50	50	50	50	49	50	50	50	50	50	50	49	50

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.9.10 **There Was A Strong, Significant Correlation Between PainDETECT And The SCL-90-R Somatisation Domain.**

There was a strong, significant correlation between painDETECT and SCL-90-R Somatisation scores (see Table 23 for r and significance values).

3.4.9.11 **There Were Moderate, Significant Correlations Between PainDETECT And The Following SCL-90-R Domains.**

There were moderate, significant correlations between painDETECT and the following domains of the SCL-90-R (see Table 23 for r and significance values): Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Phobic-Anxiety, Paranoid Ideation, Psychoticism, Positive Symptom Total and the Global Severity Index.

There were no significant relationships between painDETECT and SCL-90-R domains of Hostility and Positive Symptom Distress Index (see Table 23 for r and significance values).

3.4.9.12 **PainDETECT And EPQ-R**

Table 24: painDETECT and EPQ-R correlations.

	PainDETECT	EPQ-R-E	EPQ-R-N	EPQ-R-P
Pearson Correlation	1	-0.15	.284*	0.181
Sig. (2-tailed)		0.303	0.048	0.213
N	50	49	49	49

* Correlation is significant at the 0.05 level (2-tailed).

There was a weak, significant correlation between painDETECT and the EPQ-R-N domain only (see Table 24 for r and significance values).

3.4.9.13 **PainDETECT And STAI**

Table 25: painDETECT and STAI state and trait correlations.

	PainDETECT	STAI_State	STAI_Trait
Pearson Correlation	1	.407**	.318*
Sig. (2-tailed)		0.003	0.024
N	50	50	50

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.9.14 There Were Moderate, Significant Correlations Between PainDETECT And Both STAI State And STAI Trait Domains.

There were moderate, significant correlations between painDETECT and both STAI state and STAI trait domains (see Table 25 for r and significance values).

3.4.10 NRS Pain Scores On The Day Of Scanning Correlations.

Table 26: Pain on the day and correlations with pain duration and CES-D

	Pain-day	Duration (months)	CES-D
Pearson Correlation	1	0.041	.437**
Sig. (2-tailed)		0.779	0.002
N	50	50	50

** Correlation is significant at the 0.01 level (2-tailed).

3.4.10.1 There Was A Moderate, Significant Correlation Between Pain On The Day Of Scanning And Depression Scores.

There was a moderate, significant correlation between pain on the day of scanning and depression scores (see Table 26 for r and significance values).

3.4.10.2 NRS Pain Scores On The Day Of Scanning And SF-36

Table 27: Pain on the day and SF-36 correlations.

There were moderate, significant correlations with pain on the day of scanning and SF-36 domains of Social Functioning, Bodily Pain, Mental Health, Role-Emotional, Vitality and Mental Component Summary

	Pain on scanning day	Physical Function	Social Function	Role-Physical	Bodily Pain	Mental Health	Role-Emotional	Vitality	General Health Perception	PCS	MCS
Pearson Correlation	1	-0.274	-.393**	-0.118	-.314*	-.375**	-.320*	-.340*	-0.197	-0.268	-.432**
Sig. (2-tailed)		0.056	0.005	0.42	0.028	0.008	0.025	0.017	0.176	0.063	0.002
N	50	49	49	49	49	49	49	49	49	49	49

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.10.3 There Were Moderate, Significant Correlations With Pain On The Day Of Scanning And The Following SF-36 Domains.

There were moderate, significant correlations with pain on the day of scanning and the following SF-36 domains (see Table 27 for r and significance values): Social Functioning, Bodily Pain, Mental Health, Role-Emotional, Vitality and the Mental Component Summary.

NRS Pain Scores On The Day Of Scanning And SFMPQ

Table 28: Pain on the day and SFMPQ correlations.

	Pain on scanning day	Sensory Pain Descriptors	Affective Pain Descriptors	VAS	Present Pain Intensity
Pearson Correlation	1	.342*	0.004	.543**	0.204
Sig. (2-tailed)		0.017	0.983	<0.001	0.169
N	50	48	35	48	47

** Correlation is significant at the 0.01 level (2-tailed).

3.4.10.4 There Was A Strong, Significant Correlation Between Pain On The Day Of Scanning And SFMPQ VAS.

There was a strong, significant correlation between pain on the day of scanning and SFMPQ VAS (see Table 28 for r and significance values).

3.4.10.5 There Was A Moderate, Significant Correlation Between Pain On The Day Of Scanning And SFMPQ Sensory Pain Descriptors.

There was a moderate, significant correlation between pain on the day of scanning and SFMPQ sensory pain descriptors (r = .342, n = 48, p = 0.017) (see Table 28 for r and significance values).

3.4.10.6 NRS Pain Scores On The Day Of Scanning And SCL-90-R

	Pain on scanning day	Somatisation	Obsessive-Compulsive	Interpersonal Sensitivity	Depression	Anxiety	Hostility	Phobic Anxiety	Paranoid Ideation	Psychoticism	Global Severity Index	Positive Symptom Total	Positive Symptom Distress Index
Pearson Correlation	1	.462**	.366**	.335*	.287*	.381**	0.244	.296*	.305*	.352*	.419**	.400**	.280*
Sig. (2-tailed)		0.001	0.009	0.017	0.045	0.006	0.087	0.037	0.031	0.012	0.002	0.004	0.049
N	50	50	50	50	49	50	50	50	50	50	50	49	50

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 29: Pain on the day and SCL-90-R correlations.

There were moderate to weak, significant correlations between pain on the day of scanning and domains of Somatisation, Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Phobic-Anxiety, Paranoid Ideation, Psychoticism, Global Severity Index (GSI), Positive Symptom Total and Positive Symptom Distress Index.

3.4.10.7 There Were Moderate To Weak, Significant Correlations Between Pain On The Day Of Scanning And The Following Domains Of The SCL-90-R.

There were moderate to weak, significant correlations between pain on the day of scanning and the following domains of the SCL-90-R (see Table 29 for r and significance values): Somatisation, Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Phobic-Anxiety, Paranoid Ideation, Psychoticism, Global Severity Index (GSI), Positive Symptom Total, Positive Symptom Distress Index. There was no significant relationship with pain on the day of scanning and SCL-90-R Hostility domain.

3.4.10.8 NRS Pain Scores On The Day Of Scanning And STAI

Table 30: Pain on the day of scanning and STAI scores correlations.

	Pain on scanning day	STAI_State	STAI_Trait
Pearson Correlation	1	.309*	0.225
Sig. (2-tailed)		0.029	0.116
N	50	50	50

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.10.9 There Was A Moderate, Significant Correlation Between Pain On The Day Of Scanning And STAI State Scores.

There was a moderate, significant correlation between pain on the day of scanning and STAI State scores but not with STAI trait scores (see Table 30 for r and significance values).

3.4.11 CES-D Correlations

3.4.11.1 CES-D And SF-36

Table 31: CES-D and SF-36 correlations.

There were strong, significant correlations with pain on the day of scanning and domains of Social Functioning, Mental health, Vitality, Physical Component Summary, General Health, Mental Component Summary

	CES-D	Physical Function	Social Function	Role-Physical	Bodily Pain	Mental Health	Role-Emotional	Vitality	General Health Perception	PCS	MCS
Pearson Correlation	1	-.476**	-.641**	-.409**	-.453**	-.694**	-.483**	-.732**	-.545**	-.600**	-.747**
Sig. (2-tailed)		0.001	<0.001	0.004	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
N	50	49	49	49	49	49	49	49	49	49	49

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.11.2 There Were Strong, Significant Correlations With CES-D Scores And The Following SF-36 Domains.

There were strong, significant correlations with CES-D scores and the following SF-36 domains: Social Functioning, Mental health, Vitality, Physical Component Summary, General Health, Mental Component Summary (see

Table 31 for r and significance values).

3.4.11.3 There Were Moderate, Significant Correlations With CES-D Scores And The Following SF-36 Domains.

There were moderate, significant correlations with CES-D Scores and the following SF-36 domains:Physical Functioning, Role-Physical, Bodily Pain, Role-Emotional (see

Table 31 for r and significance values).

3.4.11.4 CES-D And SFMPQ

Table 32: CES-D and SFMPQ correlations.

	CES-D	Sensory Pain Descriptors	Affective Pain Descriptors	VAS	Present Pain Intensity
Pearson Correlation	1	.564**	.457**	.364*	0.194
Sig. (2-tailed)		<0.001	0.006	0.011	0.191
N	50	48	35	48	47

** Correlation is significant at the 0.01 level (2-tailed).

3.4.11.5 There Was A Strong, Significant Correlation Between CES-D Scores And SFMPQ Sensory Pain Descriptors.

There was a strong, significant correlation with CES-D Scores and SFMPQ sensory pain descriptors (see Table 32 for r and significance values).

3.4.11.6 There Were Moderate, Significant Correlations Between CES-D Scores And SFMPQ Affective Pain Descriptors And Between SFMPQ VAS.

There were moderate, significant correlations between CES-D Scores and SFMPQ affective Pain Descriptors and between SFMPQ VAS (see Table 32 for r and significance values). CES-D And SCL-90-R

Table 33: CES-D and SCL-90-R correlations.

There were strong, significant correlations between CES-D scores and the following domains of SCL-90-R: Somatisation, Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic-Anxiety, Paranoid Ideation, Psychoticism, Global Severity Index, and Positive Symptom Total and a moderate, significant correlation with the Positive Symptom Distress Index

	CES-D	Somatisation	Obsessive-Compulsive	Interpersonal Sensitivity	Depression	Anxiety	Hostility	Phobic Anxiety	Paranoid Ideation	Psychoticism	Global Severity Index	Positive Symptom Total	Positive Symptom Distress Index
Pearson Correlation	1	.663**	.758**	.696**	.739**	.726**	.572**	.709**	.557**	.705**	.805**	.714**	.489**
Sig. (2-tailed)		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
N	50	50	50	50	49	50	50	50	50	50	50	49	50

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.11.7 There Were Strong, Significant Correlations Between CES-D Scores And The Following Measures Of The SCL-90-R.

There were strong, significant correlations between CES-D scores and the following measures of the SCL-90-R: Somatisation, Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic-Anxiety, Paranoid Ideation, Psychoticism, Global Severity Index and Positive Symptom Total (see Table 33 for r and significance values).

3.4.11.8 There Was A Moderate, Significant Correlation Between CES-D Scores And The SCL-90-R Positive Symptom Distress Index.

There was a moderate, significant correlation between CES-D scores and the SCL-90-R Positive Symptom Distress Index (see Table 33 for r and significance values). CES-D And STAI

Table 34: CES-D and STAI correlations.

	CES-D	STAI_State	STAI_Trait
Pearson Correlation	1	.692**	.668**
Sig. (2-tailed)		<0.001	<0.001
N	50	50	50

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

3.4.11.9 There Were Strong, Significant Correlations Between CES-D Scores And Both STAI State And STAI Trait Domains.

There were strong, significant correlations between CES-D scores and both STAI state and STAI trait domains (see Table 34 for r and significance values).

3.4.11.10 CES-D And EPQ-R

3.4.11.11 There Was A Strong, Significant Correlation Between CES-D Scores And EPQ-R Neuroticism Domain Questionnaire.

Table 35: CES-D and EPQ-R correlations.

	CES-D	EPQ-R-E	EPQ-R-N	EPQ-R-P
Pearson Correlation	1	-0.269	.653**	0.235
Sig. (2-tailed)		0.062	<0.001	0.104
N	50	49	49	49

* Correlation is significant at the 0.05 level (2-tailed).

There was a strong, significant correlation between CES-D scores and the neuroticism domain of the EPQ-R questionnaire (see Table 35 for r and significance values).

3.5 **Results: Clinical examination**

3.5.1 **TTD Examination Scores**

A one-way between groups analysis of variance (ANOVA) was used to explore differences between groups in TTD examination scores. There was a statistically significant difference in TTD examination scores between groups (F (2,62) = 6.45, p=.003) (see Table 36)

Table 36: Mean TTD scores for Controls, MLBP and NuLBP groups.

Group	N	TTD Mean	Std. Deviation
Controls	18	2.70	0.67
MLBP	24	2.85	0.78
NuLBP	23	3.48	0.78

3.5.2 **CLBP Demonstrate An Increase In TTD Compared To Controls.**

Using planned comparisons, we observed that TTD examination scores revealed significantly increased sensory thresholds to tactile stimulation in CLBP patients compared to controls (t (62) = 2.23, p = .029) (see Table 36, Figure 33).

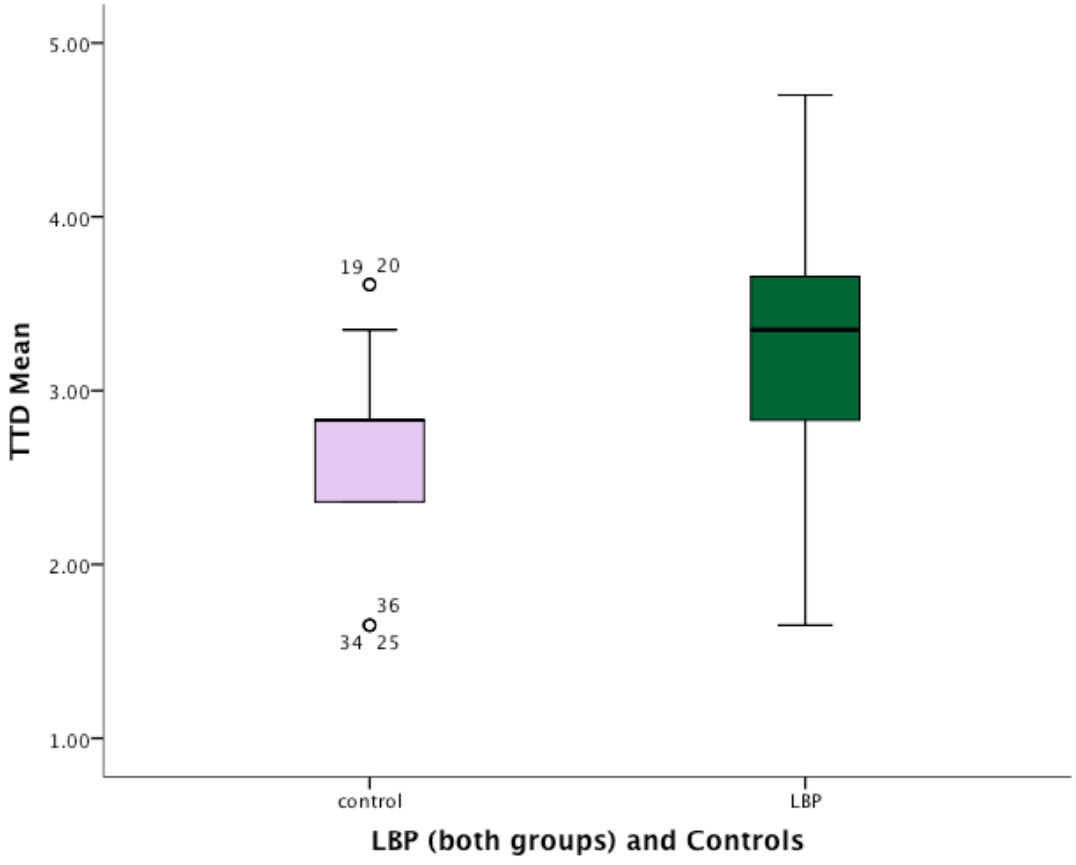

Figure 33: TTD values, LBP & Controls

Circles represent ID and scores for outliers.

3.5.3 **NuLBP Demonstrate An Increase In TTD Compared To MLBP.**

Using planned comparisons, we observed that TTD examination scores revealed significantly increased sensory thresholds to tactile stimulation in NuLBP compared to MLBP patients ($t(62) = -2.84$, $p = .006$) (see Table 36, Figure 34). In order to examine the relative influence of each LBP sub-group, we also analysed the ANOVA post hoc comparisons (Tukey HSD). We found significant differences between the Controls and the NuLBP group ($p = .005$) but not between Controls and the MLBP subjects ($p = .79$). These data suggest that the observed differences between the Controls and CLBP subjects are primarily driven by the increased sensory thresholds observed in NuLBP patients.

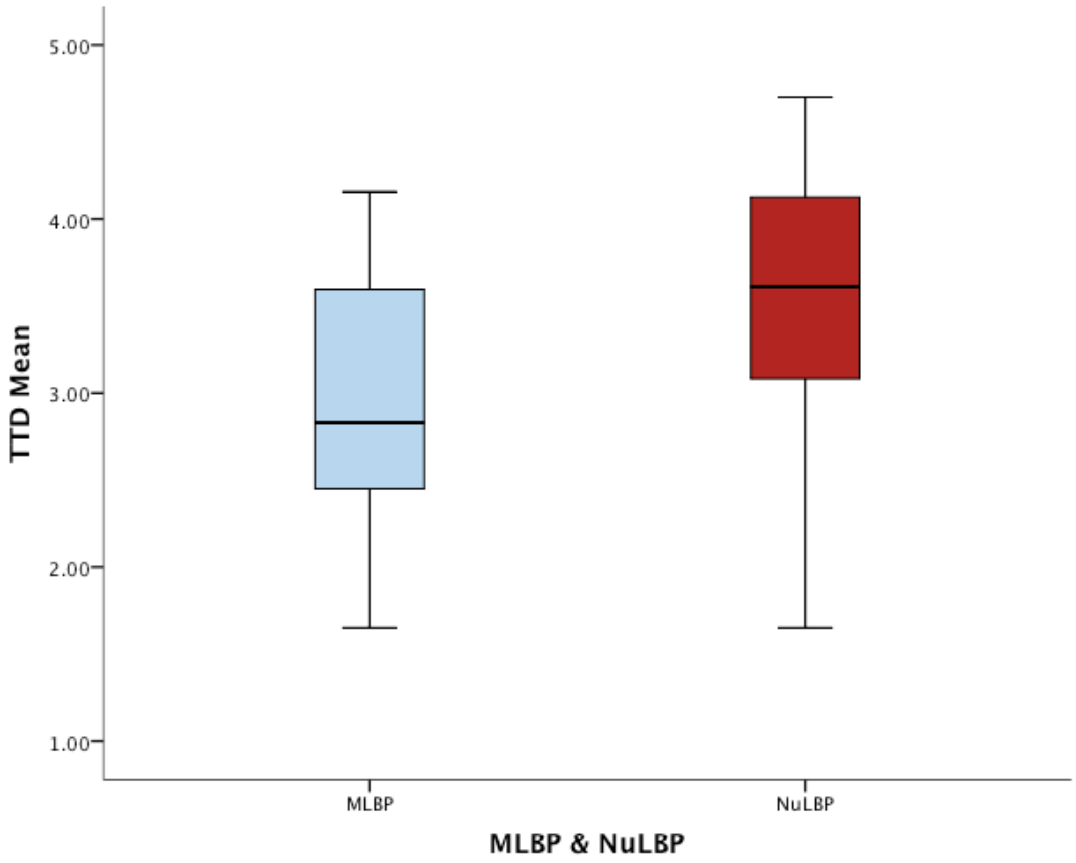

Figure 34: Mean TTD scores, MLBP & NuLBP groups.

3.5.4 **2PD Examination Scores**

Using a one-way analysis of variance (ANOVA) we were able to show significant statistical differences in 2PD examination scores between groups (F (2,62) = 5.37, p=.007) (see Figure 35, Table 37).

Table 37: Mean 2PD scores for Controls, MLBP and NuLBP groups

Group	N	2PD Mean	Std. Deviation
Controls	18	4.98	0.65
MLBP	24	6.43	1.81
NuLBP	23	6.46	1.89

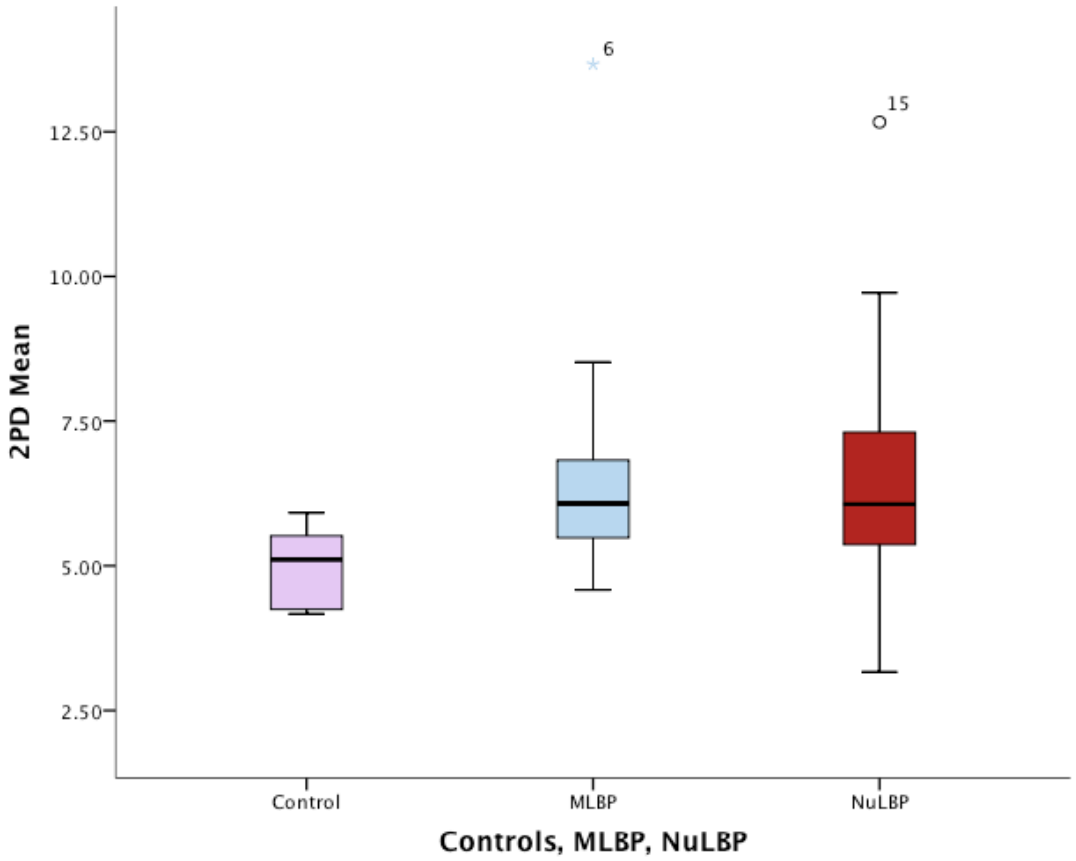

Figure 35: Mean 2PD scores for Controls, MLBP and NuLBP groups.

Circles represent ID and scores for outliers. Asterisks represent ID and scores for extreme values.

3.5.5 **CLBP Demonstrate An Increase In 2PD Thresholds Compared To Controls**

Using planned comparisons, we observed significantly increased thresholds to two-point discrimination in CLBP patients compared to controls (t (62) = -3.28, p = .002) (see Figure 36). Our results for 2PD are consistent with previous studies (Moseley 2008, Wand, Di Pietro et al. 2010, Luomajoki and Moseley 2011).

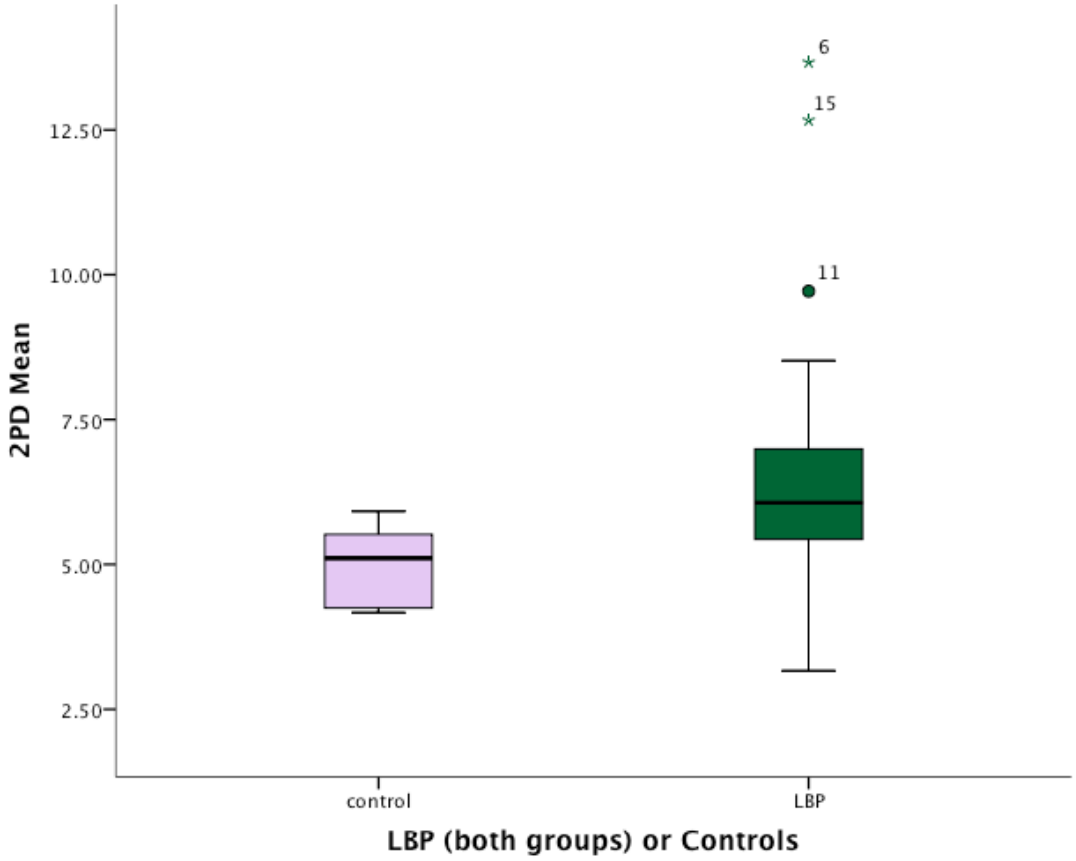

Figure 36: 2PD values, LBP & Controls.

Circles represent ID and scores for outliers. Asterisks represent ID and scores for extreme values.

In order to examine the relative influence of each LBP sub-group, we analysed the ANOVA post hoc comparisons (Tukey HSD). We found significant differences (p =. 014) between both the Controls (M = 4.98, SD = .65) and the NuLBP (M = 6.46, SD = 1.89, group and between Controls and the MLBP subjects (M = 6.43, SD = 1.81) (p =. 015), which suggests a relatively even contribution to the observed differences between the Controls and CLBP.

3.5.6 There Are No Differences In 2PD Thresholds Between NuLBP And MLBP.

Using planned comparisons, we observed no significant differences between NuLBP and MLBP groups in 2PD examination scores (t (62) = -.06, p =.952).

3.5.7 Location Of LBP Has No Effect On TTD Scores.

Table 38: Mean TTD scores according to LBP location.

LBP location	N	TTD Mean	Std. Deviation
Central	13	3.29	0.67
Left	4	3.32	1.06
Right	4	3.89	0.32
L & R	26	2.96	0.89
Total	47	3.16	0.83

We used a one-way analysis of variance (ANOVA) to examine whether mean TTD scores varied according to subjects' location of low back pain. We found no statistical differences in TTD examination scores between subjects' locations of low back pain: F (3,43) = .1.753, p=.171 (see Table 38)

3.5.8 **Location Of LBP Has No Effect On 2PD Scores**

Table 39: Mean 2PD scores according to LBP location

LBP location	N	2PD Mean	Std. Deviation
Central	13	6.21	0.89
Left	4	6.65	1.37
Right	4	5.99	1.48
L & R	26	6.60	2.28
Total	47	6.44	1.83

We used a one-way analysis of variance (ANOVA) to examine whether 2PD scores varied according to subjects' location of low back pain. We found no statistical differences in 2PD examination scores between subjects' locations of low back pain: $F(3,43) = .221$, $p = .881$ (see Table 39).

3.5.9 **Location Of Referred Leg Pain Has No Effect On TTD Scores.**

Table 40: Mean TTD scores according to leg pain location

LBP location	N	2PD Mean	Std. Deviation
LBP only	14	3.01	0.81
Above Knee	13	2.88	1.04
Below knee unilateral	12	3.56	0.44
Below knee bilateral	8	3.28	0.85
Total	47	3.16	0.83

We used a one-way analysis of variance (ANOVA) to examine whether mean TTD scores varied according to location of subjects' leg pain. We found no statistical differences in mean TTD examination scores between locations of subjects' leg pain ($F(3,43) = .1.670$, p=.188) (see Table 40).

3.5.10 Location Of Referred Leg Pain Has No Effect On 2PD Scores

Table 41: Mean 2PD scores according to leg pain location

LBP location	N	2PD Mean	Std. Deviation
LBP only	14	6.16	1.04
Above Knee	13	6.70	2.25
Below knee unilateral	12	6.48	2.51
Below knee bilateral	8	6.45	1.06
Total	47	6.44	1.83

We used a one-way analysis of variance (ANOVA) to examine whether mean 2PD scores varied according to location of subjects' leg pain. We found no statistical differences in mean TTD examination scores between locations of subjects' leg pain ($F(3,43) = .187$, $p=.904$) (see Table 41).

3.5.11 Correlation Analysis: Tactile Threshold Discrimination

3.5.11.1 CLBP Patients Demonstrate Moderate Relationships Between TTD Scores And Pain Phenotype And TTD Scores And Pain Intensity.

Table 42: Correlations between TTD scores and pain intensity, pain duration and painDETECT scores

	TTD	pain intensity	pain duration	painDETECT
Pearson Correlation	1	.354*	-0.002	.390**
Sig. (2 tailed)		0.015	0.987	0.007
N	47	47	47	47

* Correlation is significant at the < 0.05 level (2-tailed).
** Correlation is significant at the < 0.01 level (2-tailed).

We found a moderate relationship between TTD scores and numerical rating scale pain intensity measured on the day of scanning (r = 354, n = 47, p < .05) and also between TTD scores and pain phenotype (PainDETECT) (r = .390, n = 47, p = <. 01). There was no significant relationship between pain duration and TTD scores (r = .002, n = 47, p = .987) (see Table 42).

3.5.11.2 CLBP Patients Demonstrate A Moderate Relationship Between TTD Scores And STAI State Scores And TTD Scores And CES-D Scores.

Table 43: TTD correlations with STAI State & Trait & CES-D scores in CLBP patients.

	TTD	CES-D	STAI state	STAI trait
Pearson Correlation	1	.327*	.417**	0.15
Sig. (2-tailed)		0.025	0.004	0.314
N	47	47	47	47

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

We chose to investigate relationships between sensory testing thresholds with measures of anxiety and depression as these are important psychological variables implicated in the maintenance and augmentation of chronic pain states (Linton 2000, Linton 2011). We found a moderate relationship between TTD scores and CES-D scores ($r = 327$, $n = 47$, $p < .05$) and also between TTD scores and STAI state scores ($r = .417$, $n = 47$, $p = .0004$). There was no significant relationship between TTD scores and STAI trait scores ($r = .15$, $n = 47$, $p = .314$) (see Table 43).

3.5.12 Correlation Analysis: Two-Point Discrimination

3.5.12.1 CLBP Patients Demonstrate No Significant Relationships Between 2PD Scores And Pain Phenotype, Pain Intensity Or Pain Duration.

Table 44: Correlations between 2PD scores and pain intensity, pain duration and painDETECT scores.

	2PD	pain intensity	pain duration	painDETECT
Pearson Correlation	1	0.148	0.135	-0.018
Sig. (2-tailed)		0.32	0.366	0.902
N	47	47	47	47

There were no significant relationships between 2PD scores and pain intensity (r = .148, n = 47, p = .32), pain duration (r = .135, n = 47, p = .366)., or pain phenotype (r = .018, n = 47, p = .902) (see Table 44).

3.5.12.2 CLBP Patients Demonstrate A Moderate Relationship Between 2PD Scores And STAI State Scores.

Table 45: 2PD correlation with STAI State & Trait & CES-D scores in CLBP patients.

	2PD	CES-D	STAI state	STAI trait
Pearson Correlation	1	0.252	.348*	0.122
Sig. (2-tailed)		0.087	0.017	0.414
N	47	47	47	47

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

We found a moderate relationship between 2PD scores and STAI state scores (r = .348, n = 47, p = .017). There was no significant relationship between 2PD scores and STAI trait scores (r = .122, n = 47, p = .414). or 2PD scores and CES_D scores (r = .252, n = 47, p = .087) (see Table 45).

3.6 Summary: Pain and Psychometric Questionnaire data

The questionnaire data used in this study can be broadly divided in to three main dimensions:

1) Measures of the sensory discriminative dimensions of pain - bodily pain and intensity

2) Self-reported functional measures – how pain interferes with normal physical and social functioning

3) Measures of psychological well-being and distress

We hypothesised that patients with CLBP would exhibit:

1) Poorer quality of life and 2) greater psychological distress compared to controls (We chose not to assess differences in pain intensity and pain description between CLBP subjects and controls, as our controls were pain-free).

In addition, we hypothesised that patients with NuLBP would complain of 1) greater pain, 2) poorer quality of life and 3) greater psychological distress compared to MLBP patients.

Our data show that all these hypotheses are correct.

3.6.1 **CLBP Results Summary**

We saw significant differences in between CLBP subjects and controls in health related quality of life, as measured by all domains of the SF-36 (see section 3.4.3.2) Interestingly, although we chose CLBP patients with no self-report of psychological problems or mental illness, both physical and mental domains of the questionnaire were equally affected. CLBP patients obviously perceived their bodily pain to worse than controls. They also thought that their general health was significantly poorer. Functional ability (being able to take part in usual role and social activities) was affected by both physical and mental domains (SF-36 Physical Function; SF-36 Social Function; SF-36 Role-Physical; SF-36 Role-Emotional). All mental domains of the questionnaire showed significant poorer results for back pain sufferers with significantly poorer perceptions of mental well-being and psychological distress, in addition to restrictions in function being caused by emotional problems. Overall physical and mental summary scores showed highly significant differences between groups indicating a significantly poorer physical and emotional quality of life.

We also used a broad range of questionnaires to examine if CLBP patients exhibit greater psychological distress across a broad range of psychological domains. These data show a large range of psychological sequelae to CLBP, with scores showing significantly greater psychological distress in almost all domains of the psychometric questionnaires we employed, even in domains that, at first glance, would

not particularly be associated with LBP such as SCL-90-R Obsessive-Compulsive Symptoms, Interpersonal Sensitivity, Hostility, Phobic-Anxiety, and Psychoticism, as well as SCL-90-R and CES-D Depression domains and SCL-90-R and STAI Anxiety domains. In fact, out of all questionnaire domains, only SCL-90-R paranoid ideation and EPQ-R Neuroticism and Psychoticism domains did not show any significant differences between controls and CLBP patients.

3.6.2 **NuLBP Results Summary**

1) NuLBP patients complain of significantly greater pain intensity and decrease in quality of life (see Table 46)

2) Reduced ability to engage in normal physical and social functioning (see Table 47) and

3) Significantly greater psychological distress compared to MLBP patients (see Table 48).

NuLBP patients demonstrate greater pain intensity and bodily symptoms in the following questionnaire domains:

Table 46: Questionnaire domains showing increased pain intensity and bodily symptoms in NuLBP patients compared to MLBP.

Domain
Pain on scanning day (NRS)
SF-36 Bodily pain score
SFMPQ Visual Analogue Scale (VAS)
SFMPQ Sensory Pain Descriptor Scale
SFMPQ Present Pain Intensity scale

Secondly, NuLBP patients demonstrate reduced ability to engage in normal physical and social functioning in the following questionnaire domains of the SF-36:

Table 47: SF-36 domains showing reduced ability to engage in normal physical and social functioning in NuLBP patients compared to MLBP.

SF-36 Domain
Physical Functioning
Social Functioning
Physical Component Summary

Lastly, NuLBP patients showed greater psychological distress and reduced well-being compared to MLBP patients:

Table 48: Questionnaire domains showing greater psychological distress and reduced well-being in NuLBP patients compared to MLBP.

Domain
SF-36 General Mental health
SF-36 Mental Component Summary
SF-36 Vitality
SF-36 Social Functioning
CES-D
SCL-90-R Somatisation
SCL-90-R Interpersonal Sensitivity
SCL-90-R Anxiety
SCL-90-R Psychoticism
SCL-90-R Phobic anxiety
SCL-90-R Global Severity Index
SCL-90-R Positive Symptom Total
STAI state
EPQ-R-P (psychoticism)

We were also able to demonstrate relationships between pain and psychological domains. We saw moderate to strong correlations with most psychological domains and pain intensity and painDETECT. In particular, we observed strong correlations between CES-D scores and both measures of pain and pain related function and affect but also with other psychological domains.

3.7 Discussion: Pain and Psychometric Questionnaire data

3.7.1 Patients With CLBP, Especially Patients With NuLBP, Report Greater Depression Scores

There is a significant difference between CLBP subjects and controls on the Global Severity Index (GSI), which is a summary of overall psychological distress across all domains of the SCL-90-R. These data show that CLBP has a significant negative impact on well-being and quality of life. Chronic pain patients have higher rates of generalised anxiety, post-traumatic stress disorder and alcohol abuse and depression than the general population (Demyttenaere, Bruffaerts et al. 2007). In fact, depression is second only to low back pain as a leading global cause of disability (Ferrari, Charlson et al. 2013, Hoy, March et al. 2014). This study has shown that CLBP subjects score significantly higher than controls in depressive symptomology and neuropathic back pain patients scored significantly higher again than patients with MLBP. In fact, NuLBP patients scored significantly above the cut off zone of the CES-D questionnaire (>/= 19) identifying individuals at risk of depression.

Depression is a common comorbidity for patients with CLBP (Atkinson, Slater et al. 1991, Sullivan, Reesor et al. 1992, Walsh, Homa et al. 2006). In Canada CLBP patients are three to four times more likely to suffer from major depression than the pain-free population (5.9% vs 19.8%) and the rate of major depression in CLBP patients increases in a linear fashion

with pain severity (Currie and Wang 2004). In fact, back pain has been identified as the strongest predictor of major depression after adjusting for demographics and other medical comorbidity (Currie and Wang 2004).

We observed significant correlations between pain intensity and CES-D scores, as well as CES-D and painDETECT scores, which suggests that a negative affective response is a feature of the increasing severity and neuropathic component of CLBP. Interestingly, we did not identify any relationship between pain chronicity and low mood, suggesting that the development of the affective component of CLBP is not an inevitable consequence of pain duration but rather of pain intensity. Similarly, we did not identify any relationship between duration of symptoms and painDETECT scores, suggesting that the development of the neuropathic component of CLBP is not an inevitable consequence of pain duration from mechanical towards neuropathic but that MLBP and NULBP involve different mechanisms. Other studies of mechanical and neuropathic back pain agree with our findings. Freynhagen et al. found a significantly greater depression scores in a large group (n=717) of NuLBP patients. Furthermore, a strong relationship was found between severity of depression and painDETECT scores (Freynhagen, Baron et al. 2006).

The question of whether depressive symptoms arise as a consequence of pain or whether patients develop pain due to underlying depression is unresolved. There has been extensive research on depression in chronic pain patients yet relatively little on pain in patients with a primary diagnosis of depression. A major review identified 59 studies on

depression in patients' with chronic pain compared to only 14 on pain in depressive patients (Bair, Robinson et al. 2003). We excluded patients from our study that reported any psychological or mental health issues. It is possible, however, that the findings we observed of increased levels of depression in back pain patients actually relate to underlying levels of depression prevalent in the general population. Patients with depression are twice as likely to have low back pain than those without (Croft, Papageorgiou et al. 1995). It has been suggested that treatment failures in CLBP may occur because depression has either not been diagnosed or else has been ignored in the treatment regime. Studies suggest that depression is drastically under reported in CLBP (Spitzer, Williams et al. 1994, Grevitt, Pande et al. 1998, Haggman, Maher et al. 2004). Importantly, the problem of pain and depression comorbidity may be significantly under-reported in the majority of patients that have subclinical or milder forms of depression who are likely to present to GPs and primary care providers (Bair, Robinson et al. 2003). Depressed patients may therefore be treated the same as non-depressed with negative consequences (Sullivan, Reesor et al. 1992). It has been suggested that depression has a greater impact on treatment outcomes than any other factor (Linton 2000).

Conversely, it has also been stated that the reporting of pain and its importance in the diagnosis of depression is underreported, certainly at least in relation to the attention given to psychological symptoms in patients with chronic pain (Katona, Peveler et al. 2005). In fact, more than

50% of patients with depression report somatic symptoms alone, and of those, at least 60% are pain related (Bair, Robinson et al. 2003). These patients may end up having treatment addressed at their physical symptoms alone. At the same time, patients with depression may be diagnosed with 'Somatization disorder' and run the risk of having their physical symptoms dismissed as 'non-organic', in other words, not genuine (Katona, Peveler et al. 2005). The DSM IV (Diagnostic and Statistical Manual of Mental Disorders) diagnostic criteria for Somatization disorder state "the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings". Unfortunately, such a description renders around 85% of CLBP patients diagnosed with a psychiatric disorder! Despite widespread recognition of the biopsychosocial model, this is old-fashioned biomedical dualism of the highest order. The new DSM V (Association 2013) has attempted to address this with a new diagnostic category called "Somatic Symptom and Related Disorders". The common feature of this disorder category is that individuals have "somatic symptoms associated with significant distress and impairment." The introduction to this new disorder includes the description of the diagnosis is to be made "on the basis of positive symptoms and signs (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms) rather than the absence of a medical explanation for somatic complaints" thereby acknowledging that just because the cause of symptoms is unknown does not mean that they are made up. Ultimately, the dual

prevalence of CLBP and depression in society present a challenge to those of us seeking to explore the mechanisms of either. Writing in 1992, Sullivan et al. stated “At this time, the strongest statement that can be made about the relation between pain and depression is that the two conditions frequently coexist” (Sullivan, Reesor et al. 1992). Further work is necessary to explore the mechanisms and underlying relationships of each condition.

I suggest that there is a fundamental conceptual issue with a dualistic approach to the problem of pain and depression. Indeed, there may need to be a fundamental reconceptualisation of the view that depression is solely a consequence of the burden of pain. Pain and depression, in fact, share common neurobiological supraspinal pathways involving serotonin (von Knorring and Ekselius 1994) and noradrenaline (Max, Lynch et al. 1992) and both conditions may involve lower levels of monoamine oxidase activity (von Knorring, Perris et al. 1984). Neural dysregulation of serotonin and noradrenaline may help to explain pain and depression comorbidities and may account for the success of anti-depressant medication in treating both conditions (Fishbain 2005)(Trivedi) . Furthermore, there is also increasing evidence that neuroimmune mechanisms may underlie depressive and pain comorbidities, via the direct effect of immune cells and cytokines within the CNS or via indirect mechanisms involving the vagus nerve and/or gut brain axis (Walker, Kavelaars et al. 2014).

In later sections of this thesis we use neuroimaging to examine the neural correlates of the pain and psychological symptoms we have observed in order to examine whether patients with CLBP show changes in brain areas associated with dysegulation of mood and/or pain processing.

Our findings of widespread psychological distress in CLBP patients show the importance of psychological factors in CLBP. Although pain and disability are most frequently measured in chronic back pain trials (Froud, Patterson et al. 2014) recent recommendations for outcome measures in chronic pain suggest that 'emotional functioning' should be assessed as a core domain (Turk, Dworkin et al. 2003, Dworkin, Turk et al. 2005). We have evidence here of a broad range of psychological distress in CLBP. CLBP patients and medical professionals may have different treatment goals and expectations (Georgy, Carr et al. 2009) It is important that as well as a proper physical examination, the psychological well being of patients is adequately assessed. Our data suggest that in addition to sensory-discriminative aspects of pain and disability, psychological distress may be a vitally important component of CLBP sufferers' quality of life. Further chapters of this thesis will examine functional and structural neuroimaging correlates of the pain experience.

3.7.2 Neuropathic Pain Patients Present With Not Only Greater Pain Intensity But Also Poorer Quality Of Life Across A Number Of Mental And Physical Domains.

This study reports fundamental differences in pain intensity, function and psychological comorbidities between patients and controls and between NuLBP and MLBP. These data are in accordance with several studies comparing neuropathic with non-neuropathic patients. Neuropathic patients with a variety of chronic pain conditions report significantly higher pain and disability scores, reduced quality of life and higher psychological co-morbidities compared to non-neuropathic pain patients (Rowbotham 2002, Freynhagen, Baron et al. 2006, Torrance, Smith et al. 2006, Jensen, Chodroff et al. 2007, Smith, Torrance et al. 2007, O'Connor 2009, Smith and Torrance 2012).

These data clearly show that the impact of neuropathic pain on the individual sufferer is far greater than the sensory-discriminative characteristics of the pain alone. Subjects with neuropathic pain generally respond poorly to treatment (Baron, Binder et al. 2010). These data suggest that therapies must be aimed at alleviating not only the sensory dimensions of the pain but also alleviating its psychological sequelae and restoring functional quality of life.

Studies show that the impact of neuropathic pain varies according to the condition and also to the method of evaluation of health related quality of life (Jensen, Chodroff et al. 2007). The CLBP data from this study are

consistent with Freynhagen et al. who showed the biopsychosocial impact of NuLBP compared to MLBP (Freynhagen, Baron et al. 2006). Our data also show similar findings to studies using the SF-36 to explore differences between neuropathic and non-neuropathic pain conditions in the general population (Smith, Torrance et al. 2007). However, compared to the findings of this study, our data show greatly reduced scores across nearly all SF-36 domains (only role limitations due emotional problems (SF-36 Role-Emotional) and general mental health (SF-36 Emotional well-being) had reasonably similar, albeit still lower, results) indicating more severe pain, disability and affect in all SF-36 measures in both our neuropathic and non-neuropathic population. The reason for the reduced scores in our population is unclear. Our results may demonstrate the significant burden of CLBP compared to other chronic pain conditions. In addition, our patient group was recruited in an inner city London hospital. The substantial impact across a broad range of quality of life domains may also reflect a patient population not only struggling to cope with on-going pain but also having to negotiate this burden in harsh economic and social inner-city environment. Unfortunately, this remains speculation, as I did not collect extensive socio-economic data. However, there is an extensive body of literature that suggests that the adversity of chronic pain is associated with socio-economic and educational status (Dorner, Muckenhuber et al. 2011). This could be a useful avenue for further study.

3.7.3 **Why Do Neuropathic Pain Patients Present With Not Only Greater Pain Intensity But Also Poorer Quality Of Life?**

It may be that poorer quality of life in patients with neuropathic pain is nothing more than a consequence of increased pain intensity. However, the psychological comorbidities we have shown may be an intrinsic result of the underlying disease mechanisms of neuropathic pain, which in the case of CLBP may only be loosely connected, if at all to peripheral mechanisms. For instance, it has been suggested that neuropathic pain may cause maladaptive reorganisation of higher brain centres, which are involved in multidimensional processing of mood and affect (Smith, Torrance et al. 2007).

Perhaps it is useful to question whether it is helpful to view NuLBP as a binary phenomenon, an all or nothing concept (Attal and Bouhassira 2004, Bennett, Smith et al. 2006). Perhaps a more flexible approach is required, where neuropathic pain is seen as a continuum of signs and symptoms, whose peripheral mechanisms may or may not be seen as neuropathic, rather than a fixed, all or nothing, lesion-based pathological definition. This definition therefore allows patients with supposedly non-neuropathic such as osteoarthritis (and low back pain) to be reclassified as having a significant neuropathic component regardless of the origin of their symptoms. I suggest that mechanisms may be of extreme importance in chronic neuropathic pain and differences that have been identified between groups in both sensory-discriminative examination and

questionnaire evaluation may show supraspinal neural correlates. The next sections therefore show the results of structural and functional neuroimaging of CLBP in order to highlight differences between groups to show the neural correlates of both non-neuropathic and neuropathic CLBP.

3.8 Discussion: TTD and 2PD Examination Data

3.8.1 Summary Of Main Findings

We aimed to discover whether CLBP patients demonstrated deficits in tactile threshold testing of the lower back, in order to examine the relationship of tactile acuity and CLBP and, in particular, whether deficits in tactile threshold testing of the lower back were worse in patients with NULBP compared to MLBP. We also wished to examine the relationship of pain and psychometric variables to our examination data. We found significantly higher 2PD and TTD thresholds in CLBP patients than controls. NuLBP patients had significantly higher mean TTD threshold scores than MLBP patients. There were no differences in 2PD thresholds between the NuLBP and MLBP patients. Location of LBP or referred leg pain had no bearing on 2PD or TTD scores. Moderate relationships were seen between TTD thresholds and both pain severity and pain phenotype (as measured by painDETECT) but not pain duration. Moderate relationships were also seen between TTD examination data and STAI State and depression scores. No relationships were seen between 2PD scores and pain severity, phenotype or duration. 2PD data showed a moderate relationship with STAI State scores only.

3.8.2 What Mechanisms Underlie Both The Hyposensitivity To Tactile Stimuli And Also The Increased 2PD Thresholds Seen In CLBP Patients Compared To Controls?

These tactile data may be explained by changes to the peripheral or central nervous system, or, indeed, a combination of both. Tactile threshold and 2PD testing have traditionally been used to assess the integrity of the peripheral nervous system. However, we chose these tests principally as a marker of central nervous system plasticity, in accord with other chronic pain studies (see section 3.2.2.3). Nevertheless, it is possible that the changes we observed may be driven by peripheral mechanisms. For instance, peripheral neuropathy of lumbar dorsal rami could account for both tactile hyposensitivity and also increased 2PD thresholds. However, studies on the sequelae of a compressive lesion to a mixed peripheral nerve show an order of events governed by nerve diameter size (Rydevik, Brown et al. 1984, Nygaard and Mellgren 1998, Yamashita, Kanaya et al. 2002). The first nerves to be affected by a compressive lesion are large diameter Aα fibres and the largest Aβ fibres. Damage to these fibres, which mediate vibration sense, proprioception and 2PD, may therefore be responsible for increases in 2PD thresholds. Thereafter, with increasing compression, smaller diameter Aβ fibres transducing light touch may be compromised, resulting in increases to tactile thresholds.

However, the examination data show that although NuLBP patients demonstrated increased tactile thresholds compared to MLBP patients, 2PD thresholds were unaffected, making a diagnosis of compressive neuropathy unlikely to be the cause, as one would expect a pattern of loss of 2PD first then alterations in light touch. Therefore, I suggest that involvement of central nervous system mechanisms is a more likely reason for these changes. The question that arises is what sort of involvement? In a clinical setting, increases in tactile thresholds, but not 2PD thresholds in an individual patient might suggest unwelcome pathology of the CNS, perhaps affecting transmission of sensory input via the dorsal columns. However, this is extremely unlikely to be the cause in a group of 24 patients who, apart from a diagnosis of CLBP are otherwise healthy. I suggest, therefore, that a more likely explanation is that these findings most likely reflect neuroplastic alterations to representational areas in the somatosensory cortex that were discussed in section 3.1.4 and are consistent with work showing changes in representational fields associated with alterations in.2PD thresholds (Flor 1995, Flor, Elbert et al. 1995, Lotze, Flor et al. 2001, Juottonen, Gockel et al. 2002, Maihofner, Handwerker et al. 2003, Pleger, Tegenthoff et al. 2004, Maihofner, Forster et al. 2005).

Additional supraspinal mechanisms may also explain the tactile hyposensitivity we observed. Similar results have also been demonstrated both experimentally (Nathan 1960, Apkarian, Stea et al. 1994, Moriwaki and Yuge 1999, Geber, Magerl et al. 2008, Agostinho,

Scherens et al. 2009) and also in clinical studies (Leffler, Kosek et al. 2000, Leffler, Hansson et al. 2003), including CLBP (Puta, Schulz et al. 2013). It has been suggested (Agostinho, Scherens et al. 2009) that that chronic pain causes a centrally-mediated impairment of non-painful stimuli. Patients in chronic pain may divert attentional and working memory resources to painful stimuli (Legrain, Crombez et al. 2011, Romero, Straube et al. 2013). I suggest that hyposensitivity may be part of a general coping strategy employed by the CNS that has parallels with neglect-type phenomena that are seen in CLBP and other chronic pain conditions. As pain increases, CNS resources are directed towards the painful area to deal with the situation. However, if pain persists, then the CNS may adapt by decreasing attentional mechanisms devoted to the *body* part in question, in an effort to distance oneself from the source of pain. I propose that grey matter increases (Teutsch, Herken et al. 2008) and decreases (Apkarian, Sosa et al. 2004, Schmidt-Wilcke, Leinisch et al. 2006, Ivo, Nicklas et al. 2013, Wu, Inman et al. 2013) observed in the somatosensory cortex and elsewhere in the brain in acute and chronic pain respectively may be the neural correlates of this process. However, in chronic pain conditions it appears that this adaptive strategy does not lead to pain reduction. In fact, I hypothesise that grey matter loss may, in itself, cause dysregulation of pain processing and inhibitory modulatory systems. The following chapters in this thesis will use neuroimaging to identify neuroplastic changes associated with group differences in both our questionnaire and clinical examination data in an attempt to test these hypotheses.

Chapter 4 EVALUATION OF STRUCTURAL CHANGES IN GREY MATTER IN CLBP USING VOXEL BASED MORPHOMETRY (VBM)

4.1 Introduction

Conventional methods of clinical assessment, structural imaging and diagnostic testing have failed to adequately explain the causes and underlying mechanisms for either mechanical or neuropathic CLBP (Waddell 2005, Krismer and van Tulder 2007). In the previous chapter we identified clear differences in behavioural data and sensory testing between CLBP patients and controls and between NuLBP and MLBP patients. We interpreted these findings in terms of the potential for supraspinal neuroplastic adaptions to pain. It has been claimed that functional and structural brain imaging may have utility as a diagnostic marker for CLBP, as an adjunct to conventional methods of evaluation(Apkarian, Baliki et al. 2009). This chapter will investigate this claim, using structural brain imaging, namely voxel based morphometry, to identify differences between CLBP patients and controls and differences between CLBP subgroups.

Voxel based morphometry (VBM) is a fully automatic unbiased technique which statistically analyses the volume of gray and white matter between

differing groups on a voxel to voxel basis across the whole brain using normalised, modulated data to correct for differences in brain size (Ashburner and Friston 2000). This makes it an ideal tool to assess the potential for structural neuroplastic change associated with CLBP. Both increases and decreases in grey matter have been identified in clinical populations suffering from a wide range of chronic pain conditions (May 2011, Smallwood, Laird et al. 2013). However, the exact mechanisms behind grey matter changes are as yet unknown.

4.1.1 **What Do Volume Changes Represent?**

In 2004 Apkarian et al. described findings of GM reductions in the dorsolateral prefrontal cortex and thalamus as brain atrophy, caused by neuronal cell death (Apkarian, Sosa et al. 2004). However, studies emerging over the last 5 years, showing restoration of grey matter deficits after successful treatment in a variety of conditions, including CLBP, suggest that cell death is unlikely to be the mechanism behind GM reductions in neuroimaging studies (Obermann, Nebel et al. 2009, Rodriguez-Raecke, Niemeier et al. 2009, Gwilym, Filippini et al. 2010, Seminowicz, Wideman et al. 2011). Furthermore, as some density changes appear to be reversible, this suggests that grey matter changes are also likely to be a consequence of pain, rather than a causative factor.

Most chronic pain studies show reduced GM volume, yet increases are also consistently reported (Smallwood, Laird et al. 2013). Recent

evidence shows that structural plasticity is temporally dynamic; increases in volume in brain areas associated with learning increase occur within hours both in human and animal models (Sagi, Tavor et al. 2012). In animal models, increased volume is associated with changes in the morphology of astrocytes and neurons, primarily involving enhancement of tissue organisation and reshaping of neuronal or glial processes and concomitant increased levels of brain derived neurotrophic factor (BDNF), which may be a marker of synaptic long term potentiation (Blumenfeld-Katzir, Pasternak et al. 2011, Sagi, Tavor et al. 2012). Similar synaptic mechanisms may be involved in chronic pain as well as in memory and learning (Sandkuhler 2000, Sandkuhler 2007). Peripheral nerve injury and C fibre stimulation in rodents causes increased permeability of the blood-brain and blood-spinal cord barrier after 24 hours, causing plasma extravasation throughout the spinal cord and brain, which may be another possible mechanism for initial volume increase (and possible later decrease) (Beggs, Liu et al. 2010). In humans, grey matter density increase in response to painful stimulation in areas associated with somatosensory processing has been reported after only eight days (Teutsch, Herken et al. 2008). Grey matter increases and reductions could be caused by a wide variety of possible mechanisms - a decrease in glial or neuronal cell size, changes to synaptic architecture, axonal or dendritic density or structure, local blood flow or relative levels of hydration (May and Gaser 2006, Zatorre, Fields et al. 2012). Therefore, non-neuronal mechanisms, rather than neurogenesis or cell death, are

arguably more likely to account for the increases and decreases in GM witnessed in structural imaging studies.

Similarly, it is not known what factors influence the mechanisms behind GM volume alterations in chronic pain. These may include pain intensity, pain duration, mood and cognitions, activity and lifestyle changes, co-morbidities, medication and social, cultural and environmental factors. The relevance and importance of possible causal factors to underlying mechanisms is, as yet, unknown (Tracey and Bushnell 2009).

4.1.2 **Structural Neuroimaging Studies Of CLBP**

The results of CLBP structural neuroimaging studies are varied, showing a mixed picture of both increases and decreases in grey matter in patient groups that vary both in size and clinical characteristics. Apkarian's study of 2004 described 26 individuals diagnosed with CLBP (15 'musculoskeletal', 5 radicular and 6 'mixed picture'). They reported an overall reduction in brain grey matter in the region of 5-11%. The decreased volume was related to pain duration, indicating a 1.3-cm^3 loss of grey matter for every year of chronic pain. Pain characteristics were important. A combination of sensory and negative-affective dimensions of pain (assessed by the short form McGill pain questionnaire (Melzack 1987) strongly predicted dorso-lateral prefrontal cortex (DLPFC) gray matter changes. Grey matter density was reduced in the bilateral DLPFC and right thalamus and was significantly dependent on the duration. Despite uneven groups with small sample sizes, inferences were made

regarding the presence and type (neuropathic or non-neuropathic) of chronic back pain. Neuropathic chronic back pain patients with radiculopathy were described as suffering significantly greater grey matter change than non-neuropathic back pain patients. Apkarian proposed that the decrease in grey matter density in the DLPFC was the reason that neuropathic pain conditions are more clinically more debilitating.

In a similar study, Schmidt-Wilcke et al in 2006 (Schmidt-Wilcke, Leinisch et al. 2006) in a study of 18 CLBP patients also found reductions in grey matter in the right somatosensory cortex, brainstem (dorsolateral pons) and right DLPFC with increases in the left thalamus and basal ganglia. Grey matter losses correlated with the extent of pain intensity and unpleasantness (measured by the SES, pain experience scale (Geissner 1995) but unlike Apkarian's study not with pain duration. In common with other studies previously mentioned, this suggests that distress and negative effect may have a neurobiological substrate in chronic pain states. At first, the reductions in brain morphology appear to contradict the earlier work of Flor (using MEG), which showed an increase in representational fields related to chronicity (Flor, Braun et al. 1997). However, neuroimaging studies of CRPS and PLP demonstrate that shrinking of representational fields correlates highly with intensity of pain and hyperalgesia (Flor 2003, Moseley 2007). Schmidt-Wilke et al. suggested that grey matter loss represents structural reorganization and

that Flor's MEG data represents functional reorganization; essentially two different measurements with different mechanisms.

Another study also shows reduced grey matter volume in elderly CLBP patients (Buckalew, Haut et al. 2008). Grey matter volume decreases have also been demonstrated in other chronic pain conditions such as headache, IBS (irritable bowel syndrome), FMS (fibromyalgia syndrome), CRPS and pelvic pain. Each type of pain condition appears to have its own unique characteristics in relation to activity and atrophy (May 2008).

VBM has also shown that many clinical pain conditions are also associated with increases as well as decreases in grey matter brain volume (FMS (Schmidt-Wilcke, Luerding et al. 2007) (IBS (Blankstein, Chen et al. 2010) (Pelvic pain (Schweinhardt, Kuchinad et al. 2008). As well as the reductions previously mentioned, CLBP patients have also shown an increase in thalamic and basal ganglia grey matter volume (Schmidt-Wilcke, Leinisch et al. 2006)**.** The authors offered no explanation for the increase in grey matter, other than noting that their group only included patients with axial pain, without radiating pain or radiculopathy, whereas Apkarian's group in 2004 studied a mixture of patients with and without neurological manifestations, as well as patients with pain outside of the lower back. To the best of this author's knowledge, no studies have yet correlated clinical profiles of axial and radiating back pain patients with functional and structural brain imaging. While previous studies have suggested that clinical phenotypes may have discrete and distinguishable cerebral fingerprints, these studies show a

wide diversity of results, most likely reflecting diversity in patient demographics, image pre-processing and methods of data analysis (Apkarian, Sosa et al. 2004, Schmidt-Wilcke, Leinisch et al. 2006, Schmidt-Wilcke, Luerding et al. 2007, Buckalew, Haut et al. 2008, Seminowicz, Wideman et al. 2011, Kong, Spaeth et al. 2013, Wu, Inman et al. 2013).

In particular, structural neuroimaging studies have inconsistently addressed the issue of characterisation of study populations into mechanical and neuropathic phenotypic subgroups. Some studies have included both mechanical and neuropathic cohorts (Apkarian, Sosa et al. 2004); others have excluded patients with neuropathic symptoms (Schmidt-Wilcke, Leinisch et al. 2006, Ivo, Nicklas et al. 2013, Kong, Spaeth et al. 2013). Other studies have not attempted to sub-categorise their CLBP populations at all, other than to list a structural diagnosis (Buckalew, Haut et al. 2008, Seminowicz, Wideman et al. 2011). It is therefore uncertain whether the GM changes observed in these studies are applicable to all subjects with CLBP or specific to either mechanical or neuropathic phenotypes of the study population. Better differentiation and characterisation of mechanical and neuropathic subgroups in CLBP will help to develop appropriate treatment strategies in order to improve patient outcomes.

Furthermore, a recent paper has also cast doubt on the significance of the reporting of grey matter density changes in mental health research, citing selective reporting of significant results and omission of negative

results, resulting in “excess significance bias” of published results (Ioannidis 2011). As many of the published papers in pain brain research involve small sample sizes, similar biases may also occur. There is a continuing need to test the hypothesis that brain volume changes occur in chronic low back pain and to investigate the underlying mechanisms. Therefore, the purpose of this chapter was to test the following hypotheses:

1. CLBP patients demonstrate brain morphological differences compared to controls

2. NuLBP patients demonstrate specific alterations in GM volume compared to MLBP patients.

4.2 Image Acquisition

All participants were scanned in a 3T GE Signa HDX MRI scanner (General Electric Healthcare, Milwaukee, USA) using an 8-channel receive only head coil. A high-resolution T1 weighted structural image was acquired for each subject using a spoiled gradient-recalled echo (SPGR) sequence (number slices = 196, slice thickness = 1.1mm, slice gap = 1.1mm, Repetition Time (TR) 7.012, Echo Time (TE) 2.812 (TR/TE =7/2.82 ms), Flip angle = 20°, FOV = 280 mm, matrix = 256 × 256). An additional highly detailed structural T2 fast spin-echo (FSE) scan was also acquired (Slice thickness = 2mm, Slice Gap = 2mm, Spatial positions = 72, Flip angle = 90º, FOV = 240mm^2, Repetition Time (TR) 4380, Echo

Time (TE) = 65.28 (TR/TE = 4380/65.28), Matrix = 320x320). A fast spin echo fluid-attenuated inversion-recovery (FLAIR FSE) scan was performed and subjects were radiologically assessed to exclude gross pathology.

4.3 **Data Pre-processing**

Image pre-processing and analysis were carried out using Statistical Parametric Mapping software 8 (SPM 8) (Wellcome Department of Cognitive Neurology, London, UK, 2008; *www.fil.ion.ucl.ac.uk/spm*), running under Matlab 7.12 (MathWorks, Natick, MA, USA). The pre-processing pipeline consisted of segmentation, normalization, and smoothing prior to statistical analysis using the Diffeomorphic Anatomical Registration Using Exponentiated Lie algebra (DARTEL) technique (Ashburner 2007). DARTEL was used as it offers optimal registration across subjects (Klein, Andersson et al. 2009). We followed the pre-processing strategy as detailed by Ashburner (http://www.fil.ion.ucl.ac.uk/%7Ejohn/misc/VBMclass10.pdf.).

Initial segmentation into grey, white and CSF (GM/WM/CSF) tissue classes was performed in native space using the Unified Segmentation Procedure developed by Ashburner and Friston (Ashburner and Friston 2005). “DARTEL imported” versions, used for DARTEL registration in the next step, were concurrently produced in order to make study-specific templates (see Figure 37) for illustration of pre-processing states detailed here and below). Next, an average of all native space grey and white

matter images from all subjects was created using both the segmented native space and DARTEL imported GM/WM/CSF files.

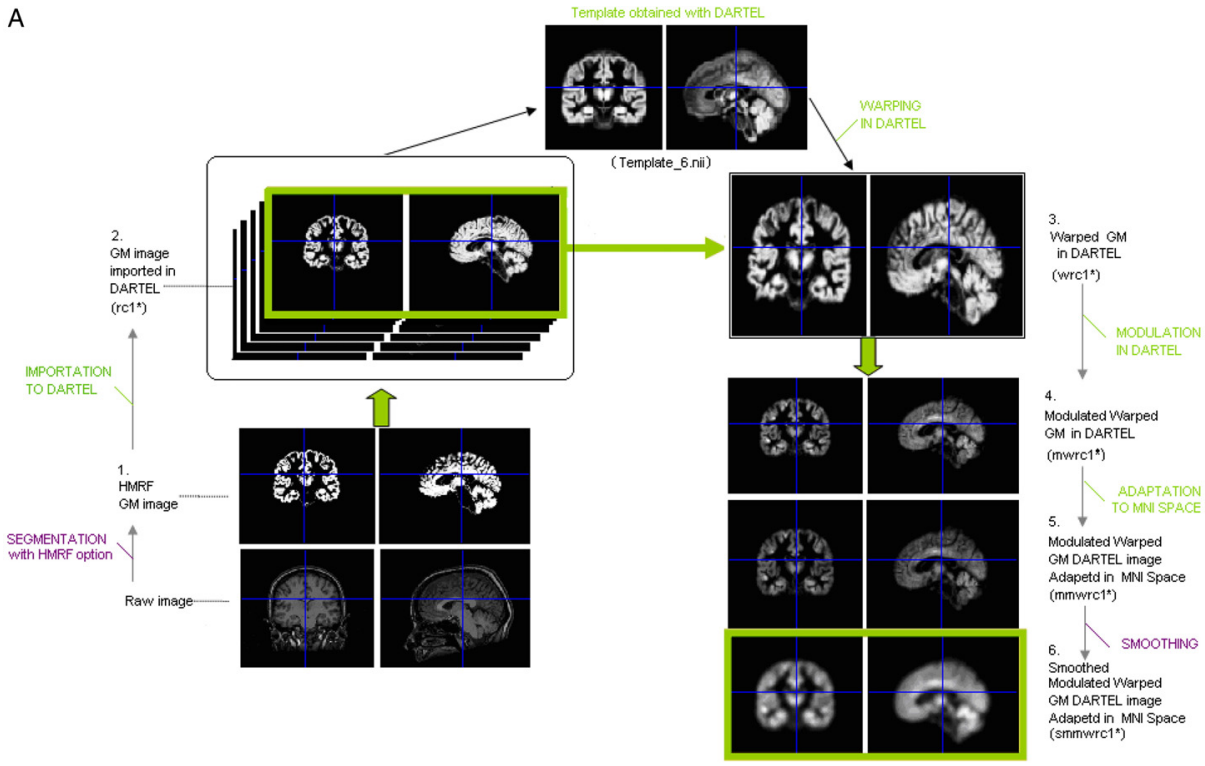

Figure 37: DARTEL pre-processing steps.

The pipeline incorporates segmentation, normalisation, modulation and smoothing (taken from (Bergouignan, Chupin et al. 2009).

An original template is generated by computing the average of all the aligned data. Each subject is then registered to the template. This creates the first iterative template. The second iteration begins with each subject registered to the first iterative template to create a second iterative template. After six iterations, the final template is generated, which is the average of the DARTEL registered data. DARTEL employs more realignment parameters (6 million as opposed to 1000 in normal VBM) to

create an optimally refined group specific template for realignment of all scans. The final template image (template 6) produced in the last sequence is the most accurate template. During iterations, all images are warped to the template, to provide a series of flow fields that parameterize deformations. These parameters are used in the normalisation and modulation step.

The final template was then registered to MNI (Montreal Neurological Institiute) space, initially using a linear affine transformation. Information from the flow fields derived from the previous iterations and the grey matter images were then applied in order to produce individual spatially normalised scans to MNI space. At this stage images were modulated to preserve local tissue volume information. Modulation accounts for variations in global and local anatomy across subjects. Without modulation, VBM is able only to compare the relative concentration or density of tissues with in area rather than absolute volume. Modulation has the effect of preserving the total amount of grey matter signal in the normalised partitions, allowing comparison of absolute volumes (ie the volume of GM is the same before and after normalization) in one area compared with another. Modulation therefore enables comparison of grey matter volume across groups.

Finally, images were spatially smoothed using an isotropic gaussian kernel (10mm Full Width at Half Maximum (FWHM)). This results in the intensity in each voxel of the smoothed data being a locally weighted average of grey and white matter density from a region of surrounding

voxels, the size of the region being defined by the size of the smoothing kernel (Ashburner and Friston 2000). There are several reasons for smoothing the data. Firstly, smoothing increases the signal to noise ratio by decreasing the intensity of isolated random-noise voxels, which otherwise may be counted as significant data. However, genuinely significant clusters, with surrounding activated voxels, will maintain their intensity signal with smoothing and still be counted as significant. Importantly, the width of the smoothing kernel should be approximately equivalent to the expected size of the expected change in brain structure/activity according to the matched filter theorem (Jones, Symms et al. 2005). Secondly, smoothing aids spatial normalisation by smoothing out anatomical differences and variations in structural anatomy to allow better registration. Consequently, smoothing compensates for the inexact nature of spatial normalisation and helps adjust for registration errors. Lastly, smoothing renders the data more normally distributed and increases the validity of parametric statistics, allowing SPM to make inferences about the data. Smoothing with a Gaussian kernel fulfils the prerequisites underpinning correction for multiple comparisons according to Gaussian Random Field theory (GRF) (Ashburner and Friston 2000).

4.4 **Statistical Analyses**

Group-level statistical analysis was performed using the general linear model (GLM) (Friston, Holmes et al. 1995, Worsley and Friston 1995). Comparisons between the 3 groups (controls, MLBP, and NuLBP) were conducted using voxelwise univariate analysis of covariance (ANCOVA)

with age and gender included as covariates of no interest in the model. Planned contrasts were used to examine group differences between the following groups: CLBP and controls; MLBP and controls; NuLBP and controls; MLBP and NuLBP. Total Intra-Cranial Volume (TIV) was included in the SPM global calculations to account for global brain volumes of different subjects (Good, Johnsrude et al. 2001, Resnick, Pham et al. 2003, Barnes, Ridgway et al. 2010, Pail, Brazdil et al. 2010).

Significant groupwise differences in GM volumes were identified following an initial height threshold of $p < 0.01$ and corrected for multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Non-stationary cluster extent correction corrects for heterogeneity in the smoothness of the height thresholded corrected t-statistic and allows for valid cluster-level inference (Hayasaka and Nichols 2004). Use of Non-stationary cluster extent correction has already been discussed in the Statistical Analysis section in Chapter 4.

The behavioural data detailed in chapter 3 show significant differences between CLBP and controls and between MLBP and NuLBP groups. Our data show differences in CES-D and STAI-state scores between all groups (there were no differences in STAI-trait scores between NuLBP and MLBP groups, however).

In order to examine the question of whether VBM group differences could be attributed to these psychological variables rather than underlying pain mechanisms, I carefully considered the statistical methods that would

allow an answer to this question. Whole-brain regression analysis of both our VBM and ASL data with CES-D and STAI-state scores was chosen, in order to examine the relationship between depression and anxiety scores and structural group differences. Whole-brain regression analysis was used, rather than post-hoc analysis of significant regions of interest, in order to avoid the pitfalls of circular data analysis (so-called “double dipping”) in which false positive results can be obtained by first obtaining data to select a subset and then undertaking further analysis of this data to obtain artificially inflated false positive results (for a full discussion of this topic see (Kriegeskorte, Simmons et al. 2009, Kriegeskorte, Lindquist et al. 2010).

I also considered using CES-D and STAI-state scores as an additional covariate in an ANCOVA analysis to “correct” and “control” for the influence of these variables in our analysis. However, as the CES-D and STAI-state scores differed between groups it was not possible to include them in an ANCOVA, as an ANCOVA cannot be used when groups differ on a covariate, as stated in Miller and Chapman’s seminal paper of 2001 (Miller and Chapman 2001).

Whole brain regression analysis of the structural data with depression and anxiety variables was performed separately for the MLBP and NuLBP groups. The results of the regression analysis were then compared to the results of the between groups ANCOVA. It was reasoned that if the regression analysis showed significant structural alterations in areas in which we also observed significant ANOVA group differences, it could be argued that the group differences in areas

common to both groups were primarily driven by the psychological variables.

4.5 Results

4.5.1 CLBP Patients Show Reduced GM Volume Compared To Controls.

LBP subjects demonstrated a widespread pattern of clusters with reduced grey matter (GM) volumes, compared to controls (see Table 49).

CLBP subjects compared to controls demonstrated significantly reduced GM volumes in the superior frontal gyrus (SFG) in the right frontal pole and in the right dorsomedial prefrontal cortex extending anteriorly (see Figure 38 and Figure 39). We observed a large cluster that extended from the left dorsolateral prefrontal cortex (DLPFC) into the left and right pregenual anterior cingulate cortex (pACC). A cluster was also identified in the right DLPFC. Reduced volumes were also seen in the left pre and post central gyrus extending in to the parietal operculum; left hippocampus; left middle temporal gyrus and right rostral (inferior) precuneus extending in to the posterior cingulate gyrus. Posteriorly, GM reductions were seen in the left occipital pole, extending into the fusiform body area in the occipital fusiform gyrus in areas V3 & 4 and right fusiform body area in the occipital fusiform gyrus. There were also two centrally located clusters that traversed right and left hemispheres in the cuneus, one inferior and one superior. The superior cluster extended into

the right lateral occipital pole. We also identified a cluster in the left lateral occipital cortex that crossed from the inferior to superior divisions.

Table 49: CLBP: GM reductions, compared to controls.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat local maxima	x	y	z	T-Stat local maxima	x	y	z
1	Posterior Cingulate	8329	-	-	-	-	2.94	15	-54	8
	Cuneus		2.75	-5	-87	36	3.03	2	-89	14
	Occipital Pole (V1)		2.75	-12	-93	8	4.30	14	-86	38
	Occipital Pole (V2)		-	-	-	-	2.90	23	-95	18
	Occipital Cortex (lateral)		-	-	-	-	3.11	39	-75	15
2	Anterior Cingulate Cortex (pregenual)	3993	3.93	-5	47	14	-	-	-	-
	Anterior mid Cingulate cortex		2.68	-11	29	18	3.29	14	26	20
	Superior Frontal Gyrus: Frontal Pole		2.94	-29	53	30	-	-	-	-
	Dorsolateral Prefrontal Cortex		-	-	-	-	3.63	29	35	39
3	Frontal Pole	3033	-	-	-	-	4.51	21	65	23
4	Occipital Fusiform gyrus	2633	4.83	-30	-78	-14	-	-	-	-
5	Middle Temporal Gyrus	822	3.48	-53	-12	-18	-	-	-	-
6	Hippocampus	783	3.87	-21	-21	-14	-	-	-	-
7	Occipital Cortex (lateral)	667	4.08	-38	-78	15	-	-	-	-
8	Postcentral Gyrus	605	3.81	-38	-15	27	-	-	-	-
9	Medial Prefrontal Cortex	34	-	-	-	-	2.67	15	39	-11

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space.

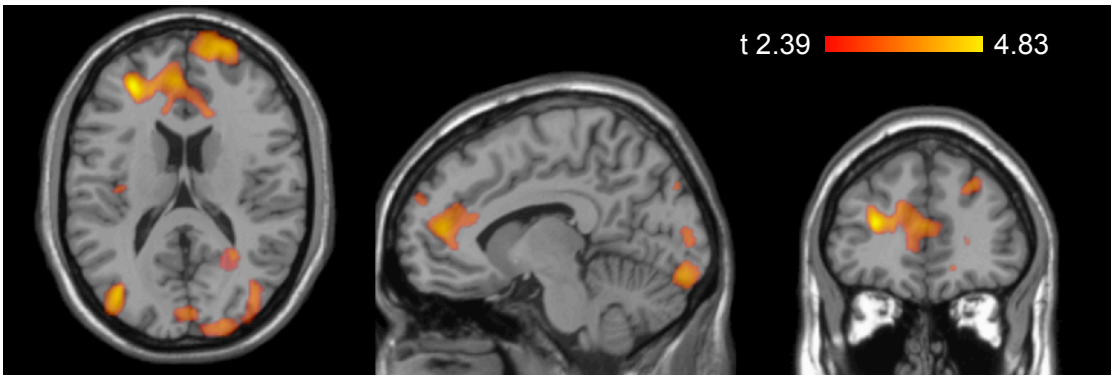

Figure 38: Reduced GM volume in CLBP subjects compared to controls

Clusters show reduced GM volume in CLBP subjects compared to controls in the right superior frontal gyrus (SFG), right dorsomedial prefrontal cortex, left and right dorsolateral prefrontal cortex (DLPFC), left and right pregenual anterior cingulate cortex (pACC), left primary motor cortex (M1), left primary sensory cortex (S1), left hippocampus; left middle temporal gyrus, right rostral precuneus, left occipital pole, left and right occipital fusiform gyrus left and right cuneus, right lateral occipital pole and left lateral occipital cortex.

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.83. The image is seen in neurological convention.

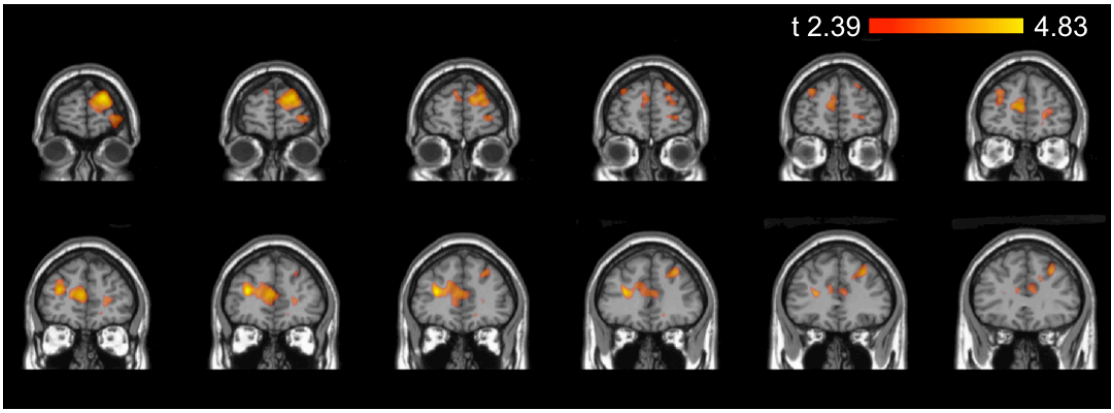

Figure 39: Reduced GM volume in CLBP subjects compared to controls

Clusters show reduced GM volume in CLBP subjects compared to controls in the right superior frontal gyrus (SFG), right dorsomedial prefrontal cortex, left and right dorsolateral prefrontal cortex (DLPFC), left and right pregenual anterior cingulate cortex (pACC), left primary motor cortex (M1), left primary sensory cortex (S1), left hippocampus; left middle temporal gyrus.

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.83. The image is seen in neurological convention.

4.5.2 CLBP Patients Show Increased GM Volume Compared To Controls.

We observed several clusters with increased GM volume (see Table 50). Anteriorly, we saw GM increases bilaterally in the lentiform nuclei, extending into the margin of the right thalamus and extending inferiorly into the nucleus accumbens (NAc) and orbitofrontal cortex (OFC) (see Figure 40 & Figure 41). We also saw a large central cluster in the brainstem extending superiorly from the upper medulla to the mid section of the pons. We observed a cluster traversing the right pre and post-central gyrus from the primary motor cortex (M1) running inferiorly and laterally and posteriorly into the primary somatosensory cortex (S1). GM volume increases were seen in clusters bilaterally spanning the superior and inferior parietal lobules. On the left, the cluster originated superiorly on the edge of the primary somatosensory cortex (S1) and ran inferiorly into the superior parietal lobule / supramarginal gyrus / angular gyrus. Much of this cluster encompassed the intra-parietal sulcus (as did the cluster on the right). Posteriorly, we saw further bilateral clusters bilaterally in the superior/inferior parietal cortex. We also identified a cluster in the right dorsal/superior precuneus.

Table 50: CLBP: Increased GM compared to controls.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat Local maxima	x	y	z	T-Stat Local maxima	x	y	z
1	Primary Motor Cortex (M1)	2582	-	-	-	-	3.27	20	-23	56
	Primary Somatosensory Cortex (S1)		-	-	-	-	3.10	24	-30	51
	Anterior intra-Parietal		-	-	-	-	3.86	29	-66	36
2	Anterior intra-Parietal	1735	3.81	-23	-56	47	-	-	-	-
3	Orbitofrontal cortex	1562	-	-	-	-	3.26	9	5	-17
	Thalamus		-	-	-	-	4.46	18	-8	3
	Lentiform Nucleus (putamen)		-	-	-	-	2.97	29	-15	-2
4	Nucleus Accumbens	946	2.60	-12	9	-12	-	-	-	-
	Lentiform Nucleus (pallidum)		2.89	-23	-3	3	-	-	-	-
5	Occipital Cortex (lateral)	562	3.30	-30	-68	20	-	-	-	-
	Superior Parietal Lobule		3.05	-26	-72	47	-	-	-	-
6	Precuneus	303	3.40	3	-59	63	-	-	-	-
7	Brainstem	295	3.75	0	-33	-41	-	-	-	-

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space.

Figure 40: Increased GM volume in CLBP subjects compared to controls

Clusters show increased GM volume in CLBP subjects compared to controls bilaterally in the lentiform nuclei, nucleus accumbens (NAc) and orbitofrontal cortex (OFC).

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.46. The image is seen in neurological convention.

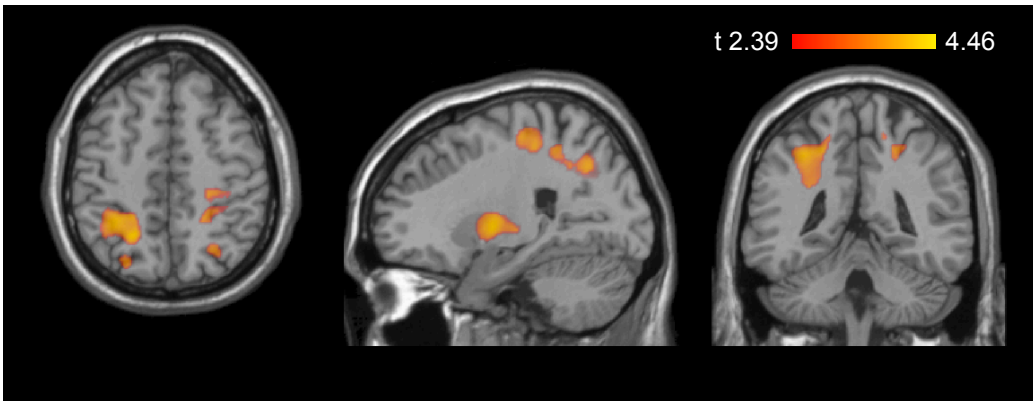

Figure 41: Increased GM volume in CLBP subjects compared to controls

Clusters show increased GM volume in CLBP subjects compared to controls in the right primary motor cortex (M1), and left and right primary somatosensory cortex (S1), superior and inferior parietal lobules and right dorsal/superior precuneus.

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.46. The image is seen in neurological convention.

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4.5.3 **MLBP And NuLBP: Individual Subgroup Analyses Compared To Controls.**

MLBP and NuLBP sub-groups showed clusters of GM increases and decreases when compared individually to controls.

4.5.3.1 **MLBP And NuLBP Patient Groups Show Reduced GM Volumes In Common Areas Compared To Controls.**

Both MLBP and NuLBP subjects compared to controls showed reductions in the left pACC, right SFG in the frontal pole, right superior cuneus, left occipital fusiform (V3/4 extra striatal body area), left inferior cuneus and left lateral occipital cortex (see Table 51, Table 52, Figure 42 & Figure 43).

Table 51: MLBP group GM reductions compared to controls

Cluster	Region	Cluster Size	Left				Right			
			T-Stat Local maxima	x	y	z	T-Stat Local maxima	x	y	z
1	Cuneus	2919	-	-	-	-	2.86	3	-87	19
	Occipital Pole (V1)		-	-	-	-	2.88	5	-93	6
	Occipital Pole (V)2		-	-	-	-	2.78	21	-95	18
2	Frontal Pole	2859	-	-	-	-	3.86	23	65	23
3	Precuneus	2776	-	-	-	-	3.39	29	-54	17
	Lateral occipital cortex		-	-	-	-	3.15	38	-71	14
4	Anterior cingulate Cortex - pregenual	1437	2.76	-5	47	14	-	-	-	-
	Dorsolateral Prefrontal Cortex	1437	5.40	-29	42	17	-	-	-	-
	Superior Frontal Gyrus: Frontal Pole	1437	2.62	-29	56	32	-	-	-	-
5	Occipital fusiform	1264	4.33	-30	-78	-12	-	-	-	-
6	Postcentral Gyrus	567	3.69	-38	-15	27				
7	Lateral Occipital Cortex	522	3.63	-38	-80	15	-	-	-	-
8	Dorsolateral Prefrontal Cortex	365	-	-	-	-	3.30	27	36	38

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space.

4.5.3.2 **Local Reductions In GM Volume Unique To MLBP Patients, Compared To Controls.**

Only MLBP subjects, compared to controls, showed reductions in the left primary somatosensory cortex into the opercular cortex; left DLPFC into the frontal pole; right DLPFC, precuneus and right posterior cingulate into the inferior/ventral precuneus (Table 51, Figure 42).

Figure 42: Reduced GM volume in MLBP subjects compared to controls.

GM reductions are seen in the left primary somatosensory cortex into the opercular cortex; left DLPFC and frontal pole; right DLPFC, precuneus and right posterior cingulate and inferior/ventral precuneus.

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.83. The image is seen in neurological convention.

4.5.3.3 **Local Reductions In GM Volume Unique To NuLBP Patients, Compared To Controls.**

Only NuLBP subjects, compared to controls, showed reductions in the left orbitofrontal cortex, hippocampus, left middle temporal gyrus, right anterior MCC and right inferior occipital pole (see Table 52, Figure 43).

Table 52: NuLBP group GM reductions compared to controls.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat Local maxima	x	y	z	T-Stat Local maxima	x	y	z
1	Anterior Cingulate Cortex (pregenual) Mid Cingulate Cortex (anterior)	4267	4.05 -	-5 -	47 -	12 -	- 3.11	- 15	- 29	- 33
2	Occipital Fusiform Gyrus	2339	4.14	-30	-78	-15	-	-	-	-
3	Cuneus Occipital Pole Lateral Occipital cortex	2188	2.52 - -	-3 - -	-89 - -	15 - -	- 3.17 2.66	- 24 48	- -96 -78	- -2 -8
3	Hippocampus Middle Temporal Gyrus	1716	3.72 3.08	-24 -53	-21 0	-14 -23	- -	- -	- -	- -
4	Frontal Pole	1401	-	-	-	-	4.18	18	65	24
5	Cuneus	643	-	-	-	-	3.71	14	-84	38
6	Orbitofrontal Cortex	523	3.08	-21	32	-26	-	-	-	-
7	Lateral Occipital Cortex	409	3.56	-38	-78	14	-	-	-	-

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space.

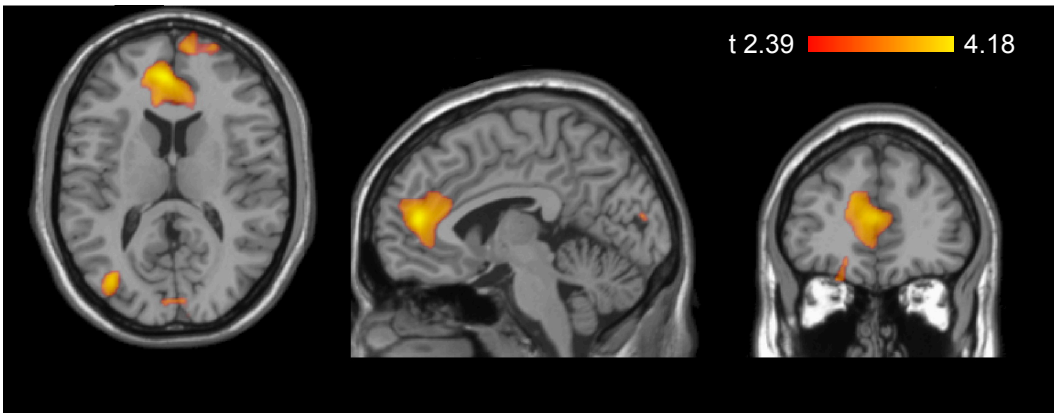

Figure 43: Reduced GM volume in NuLBP subjects compared to controls.

Reductions are seen in the left orbitofrontal cortex, hippocampus, left middle temporal gyrus, right anterior MCC and right inferior occipital pole

Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.18. The image is seen in neurological convention.

4.5.3.4 **MLBP And NuLBP Patient Groups Show Increased GM Volumes In Common Areas Compared To Controls.**

Both MLBP and NuLBP subjects, compared to controls, showed increases in the right and left superior parietal lobule and right pallidum (see Table 53, Table 54)

Table 53: MLBP GM increases compared to controls

Cluster	Region	Cluster Size	Left				Right			
			T-Stat Local maxima	x	y	z	T-Stat Local maxima	x	y	z
1	Lentiform Nucleus (Putamen)	3414	-	-	-	-	4.01	14	14	-12
	Lentiform Nucleus (Pallidum)		-	-	-	-	4.47	18	-6	2
2	Orbitofrontal cortex	1983	2.57	-14	8	-27	-	-	-	-
	Lentiform Nucleus (Putamen)		2.68	-24	15	-12	-	-	-	-
	Lentiform Nucleus (Pallidum)		2.84	-14	-2	-5	-	-	-	-
3	Premotor cortex	1892	-	-	-	-	2.67	30	-17	54
	Primary motor cortex		-	-	-	-	3.53	32	-30	51
4	Superior parietal lobule	1610	2.97	-20	-50	52	-	-	-	-
5	Superior parietal lobule	1014	-	-	-	-	3.35	33	-69	39
6	Left Cerebellum	673	3.44	-54	-45	-36	-	-	-	-

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space.

Table 54: NuLBP GM increases compared to controls.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat Local maxima	x	y	z	T-Stat Local maxima	x	y	z
1	Superior parietal lobule	1378	-	-	-	-	3.61	27	-65	36
2	Precuneus	945	-	-	-	-	4.43	3	-57	65
3	Inferior Parietal Lobule	558	-	-	-	-	3.47	44	-60	53
4	Superior parietal lobule	554	3.86	-23	-56	47	-	-	-	-
5	Brainstem	175	3.51	0	-32	-39	-	-	-	-
6	Lentiform nucleus (Pallidum)	153	-	-	-	-	3.74	18	-8	5

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space

4.5.3.5 **Local Increases In GM Volume Unique To The MLBP Group, Compared To Controls.**

MLBP subjects compared to controls alone showed increases in the right premotor cortex into M1/S1; in the right putamen (lentiform nucleus) and into the left pallidum and putamen (lentiform nucleus) extending into the nucleus accumbens and orbito-frontal cortex (see Table 53 & Figure 44).

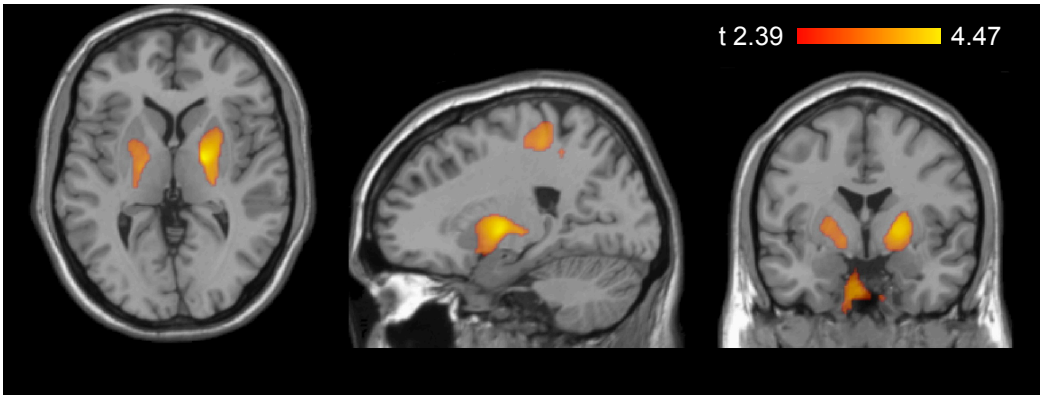

Figure 44: Increased GM volume in MLBP subjects compared to controls:

MLBP subjects show increased GM in the right and left superior parietal lobule, right premotor cortex into M1/S1); in the right and left pallidum and putamen (lentiform nucleus) and left nucleus accumbens and orbito-frontal cortex.

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.47. The image is seen in neurological convention.

4.5.3.6 **Local Increases In GM Volume Unique To The NuLBP Group, Compared To Controls.**

NuLBP subjects compared to controls alone showed increases in the brain stem and right thalamus just medial to the right lentiform nucleus, right superior precuneus just lateral to the midline and right inferior parietal lobule (see Table 54 & Figure 45).

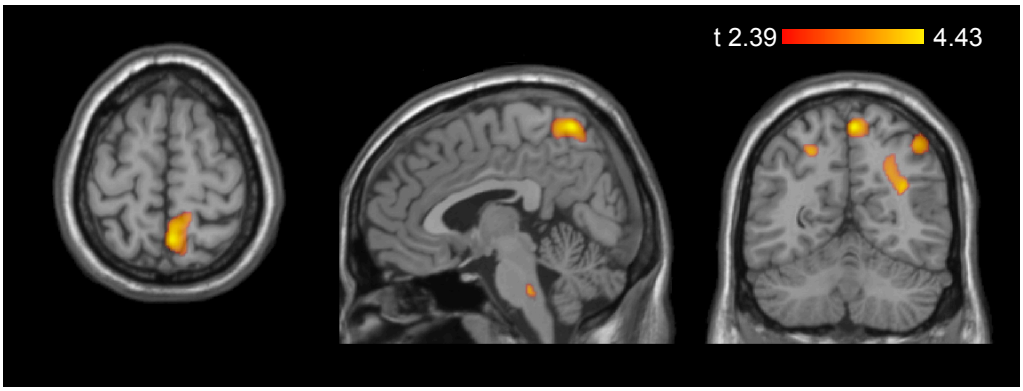

Figure 45: Increased GM volume in NuLBP subjects compared to controls.

NuLBP subjects show increases in the brain stem and right thalamus just medial to the right lentiform nucleus, right superior precuneus, right inferior parietal lobule and right and left superior parietal lobule.

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-4.43. The image is seen in neurological convention.

4.5.4 **NuLBP Patients Show Relative Reductions In GM Volume Compared To MLBP Patients.**

Compared to MLBP subjects, NuLBP subjects showed GM reductions bilaterally in the mid cingulate cortex (predominantly on the left) in a large cluster that encompassed both anterior and posterior parts of the mid cingulate cortex (MCC); in the left orbitofrontal cortex (OFC) extending laterally from the margins of the subcallosal cortex into the inferior aspect of the left insula cortex; left DLPFC and two clusters in the cerebellum, superiorly, centrally in the culmen and on the left, inferiorly in the cerebellar tonsil (see Table 55, Figure 46, Figure 47 & Figure 48).

Table 55: NuLBP GM reductions compared to MLBP.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat Local maxima	x	y	z	T-Stat Local maxima	x	y	z
1	Cerebellum	2669	3.13	-32	-59	-51	-	-	-	-
2	Orbitofrontal Cortex	777	3.53	-18	30	-30	-	-	-	-
3	Cerebellum	726	3.33	0	-62	-3	2.52	2	-42	-6
4	Mid-Cingulate Cortex	573	2.85	0	0	30	-	-	-	-
5	DLPFC	411	3.13	-26	9	27	-	-	-	-

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space.

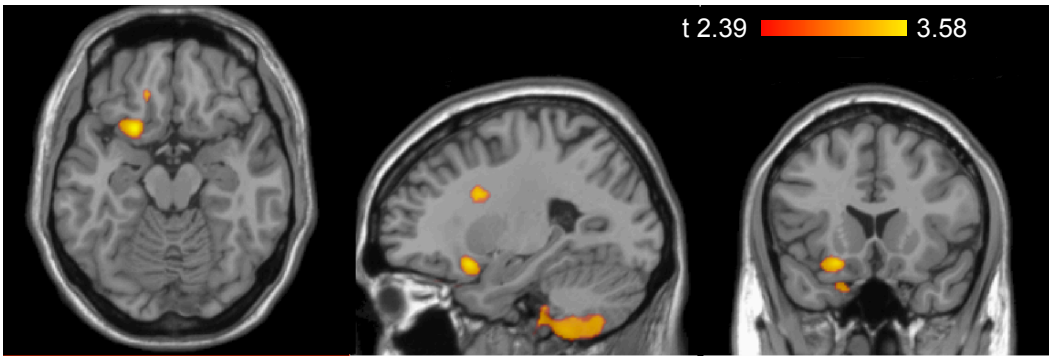

Figure 46: GM reductions in NuLBP patients compared to MLBP patients.

GM reductions are seen in the left OFC, anterior insula, DLPFC and cerebellum.

* Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.58. The image is seen in neurological convention.

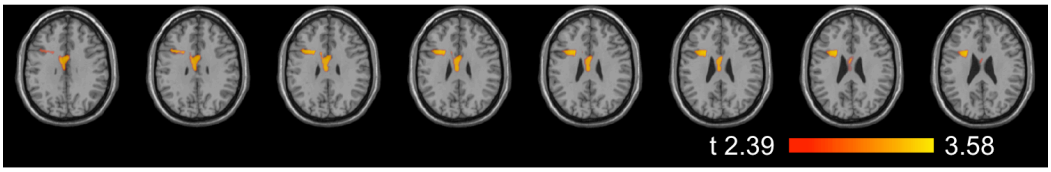

Figure 47: GM reductions in NuLBP patients compared to MLBP patients.

GM reductions are seen in the left DLPFC and bilateral mid cingulate.

* Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.58. The image is seen in neurological convention.

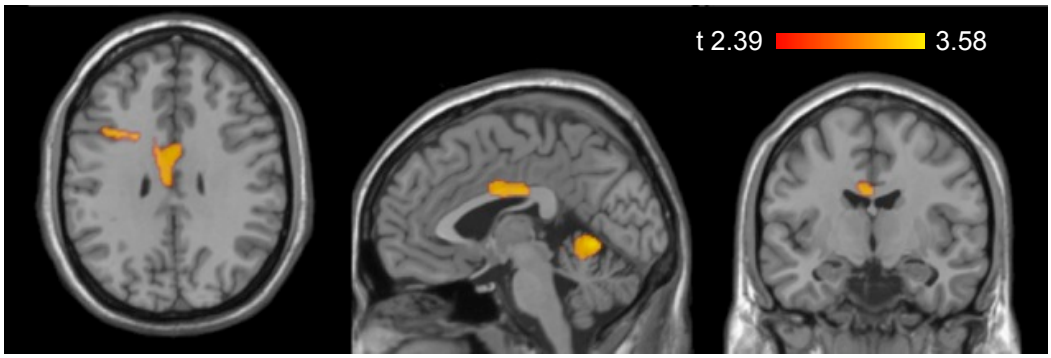

Figure 48: GM reductions in NuLBP patients compared to MLBP patients.

GM reductions are seen in the bilateral mid cingulate, DLPFC and cerebellum

* Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.58. The image is seen in neurological convention.

4.5.5 **NuLBP Patients Show Local Increases In GM Volume Compared To MLBP Patients**

Compared to MLBP subjects, NuLBP subjects showed GM increases in a cluster superiorly just to the right of the midline in the right precuneus (see Table 56, Figure 49).

Table 56: NuLBP GM increases compared to MLBP

Cluster	Region	Cluster Size	Left				Right			
			T-Stat Local maxima	x	y	z	T-Stat Local maxima	x	y	z
1	Precuneus	375	-	-	-	-	3.83	3	-56	66

* Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak voxels in the cluster; x, y, z = orientation in MNI space.

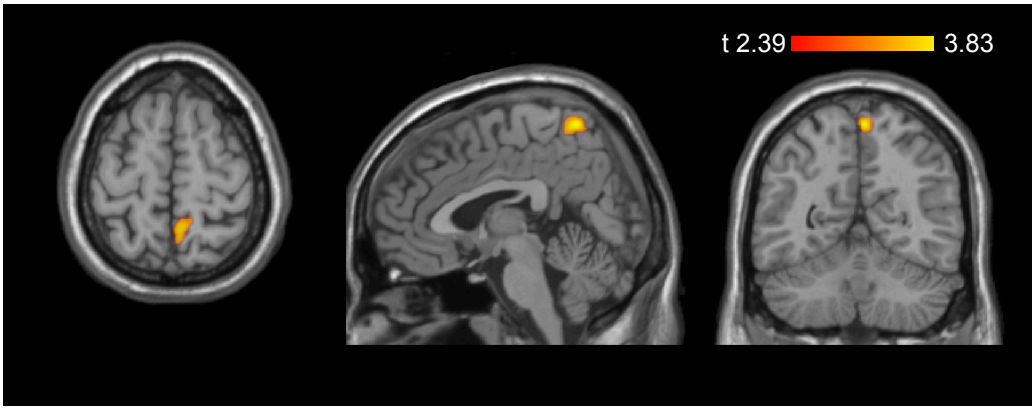

Figure 49: GM increases in NuLBP patients compared to MLBP.

NuLBP subjects show GM increases in the right precuneus.

- Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.83. The image is seen in neurological convention.

4.5.6 **Regression analysis**

4.5.6.1 **CES-D**

Comparison of regression analysis using CES-D with analysis of group differences (ANOVA) showed negligible overlap in areas in which GM alterations were observed.

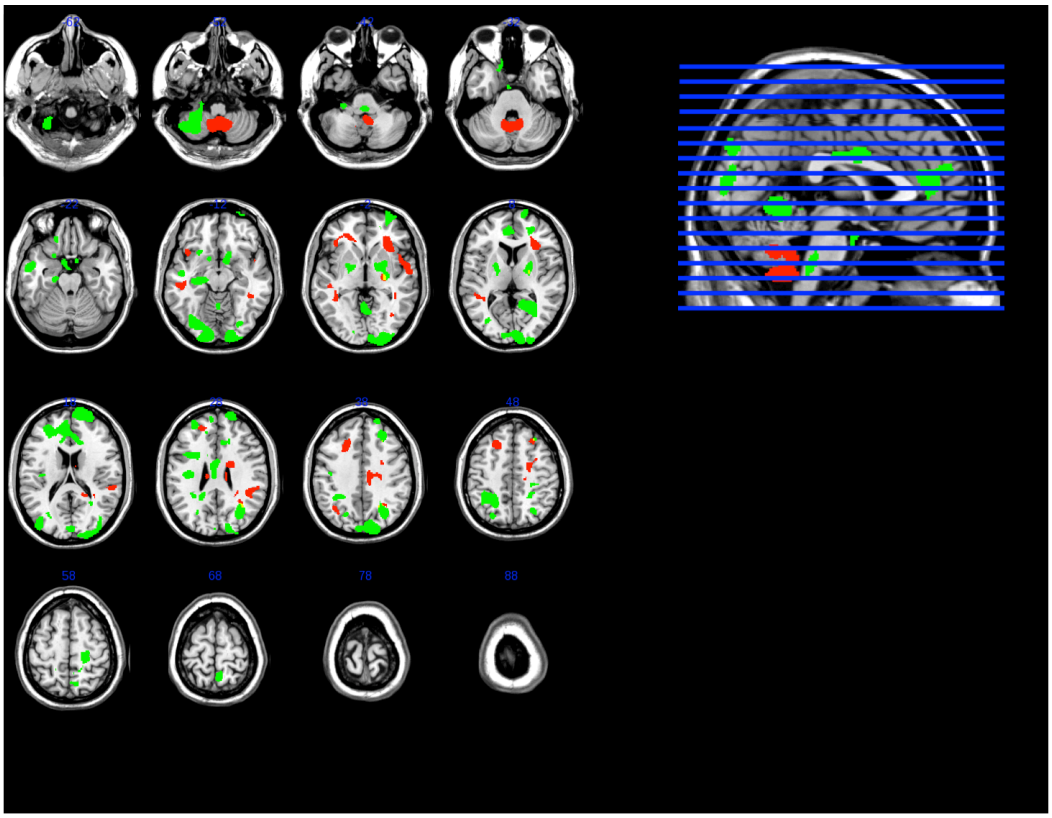

Figure 50: Composite image showing results of a) analysis of group differences (ANOVA) and b) CES-D regression analysis.

Areas in green show all significant alterations in grey matter (increases or decreases) between groups (ANOVA: CLBP & controls, MLBP & NuLBP). Areas in red show significant relationships between alterations in grey matter (increases or decreases) and CES-D scores (Regression analysis). Areas in yellow show areas of alterations in grey matter common to both analyses.

4.5.6.2 **STAI-state**

Comparison of regression analysis using STAI-state with analysis of group differences (ANOVA) showed negligible overlap in areas in which GM alterations were observed.

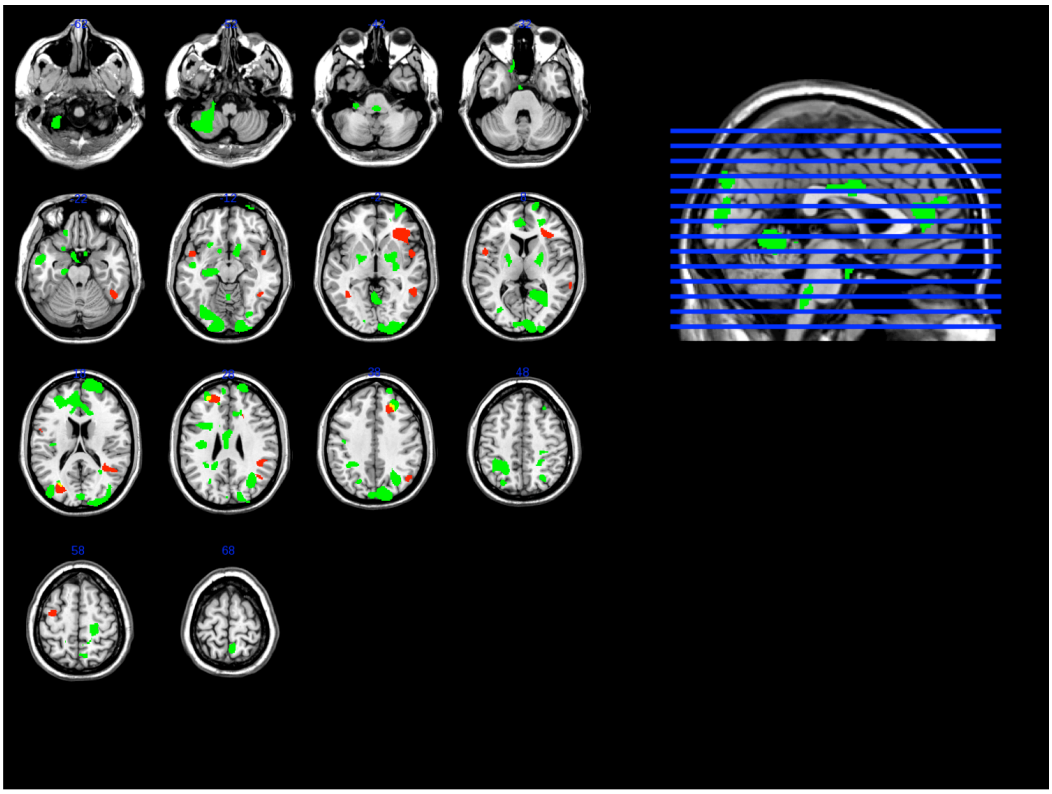

Figure 51: Composite image showing results of a) analysis of group differences (ANOVA) and b) STAI-state regression analysis.

Areas in green show all significant alterations in grey matter (increases or decreases) between groups (ANOVA: CLBP & controls, MLBP & NuLBP). Areas in red show significant relationships between alterations in grey matter (increases or decreases) and STAI-state scores (Regression analysis). Areas in yellow show areas of alterations in grey matter common to both analyses.

4.6 **Discussion**

4.6.1 **Summary Of Results**

The wide variations in patient demographics, pain intensity, duration, psychometrics and symptom profiles of our patients are an accurate representation of the heterogeneity of the CLBP clinical population. We attempted to account for these variations by including specific covariates in our analyses (Miller and Chapman 2001). Furthermore, we categorised these patients into diagnostic mechanical and neuropathic subgroups using a highly sensitive, specific and positively predictive accurate questionnaire (painDETECT) (Freynhagen 2006).

Compared to controls, CLBP subjects demonstrated significantly reduced GM volumes in the following regions: right frontal pole, bilateral dorsolateral prefrontal cortex, bilateral pregenual anterior cingulate cortex, left M1, S1, hippocampus, middle temporal gyrus, right posterior cingulate gyrus, left extrastriatal body (occipital fusiform gyrus), bilateral superior and inferior cuneus, right occipital pole and right lateral occipital cortex.

GM volume increases in CLBP compared to controls were seen in the following regions: bilateral superior and inferior parietal lobules, bilateral lentiform nucleus, bilateral nucleus accumbens, margin of the right thalamus, right orbitofrontal cortex, brainstem, right pre-motor cortex, M1, S1 and right dorsal/superior precuneus.

We were able to identify discrete morphological profiles for MLBP and NuLBP subgroups. NuLBP subjects showed GM reductions in the following regions: bilateral mid cingulate cortex (predominantly on the left), left orbitofrontal / inferior anterior insula, left DLPFC, left cerebellum. NuLBP subjects showed GM increases, compared to MLBP subjects, in the right precuneus only.

In the following section I will discuss how these findings relate to the clinical picture of CLBP and, in particular, NuLBP. Throughout, I will make reference to where changes apply to all CLBP patients (CLBP compared to controls) and where changes apply to NuLBP and MLBP sub-groups (NuLBP compared to MLBP).

I will show that clusters of GM volume alterations relate not only to the sensory discriminative experience of CLBP but also to areas devoted to cognitive-evaluative and affective-motivational aspects of the pain experience. I will show that the GM volume alterations that we have observed reflect neuroplastic changes that reflect the emotional and cognitive toll of living with persistent pain and suggest that these changes relate to concepts of disembodiment and even to a loss of self-identity. These changes have clinical importance as they strongly suggest that treatment of low back pain needs to not only target sensory aspects of pain but also cognitive and affective components, that may even cause an individual with CLBP to fundamentally re-evaluate their identity. The data suggest that that GM volume is altered in regions that are substantially involved with the following roles:

- Evaluation and assessment of internal and external stimulus saliency and decision making;

- Regulation of mood and emotional response to pain;

- Pain modulation;

- Body image;

Throughout, I discuss these themes in order of hypothesis 1 (CLBP patients demonstrate brain morphological differences compared to controls) and hypothesis 2 (NuLBP patients demonstrate specific alterations in GM volume compared to MLBP patients). Although these results show distinct differences in GM volume between NuLBP and MLBP patients, brain regions affected show considerable overlap with those observed in CLBP patients as a whole. The data suggest that all patients suffer in similar respects across all three dimensions of pain (using the model of Melzack and Casey (Melzack and Casey 1968). However, the data (and also in the behavioural data from the previous chapter) show a greater degree of suffering in patients with NuLBP. Many of the themes and brain regions are common to discussion of both hypotheses.

4.6.2 CLBP Patients Compared To Controls, And In Particular, NuLBP Patients Compared To MLBP Patients, Show GM Reductions In Areas Involved In Assessment And Evaluation Of The State Of The Body.

4.6.2.1 OFC And Insula GM Reductions In NuLBP Patients Compared To MLBP Are Evidence Of Increased Evaluation And Scrutiny Of Internally And Externally Generated Input.

I interpret GM reductions in the left orbitofrontal cortex (OFC) and anterior insula in NuLBP subjects (NuLBP compared to MLBP and NuLBP compared to controls) as a likely reflection of an ongoing state of assessment and evaluation of a hostile internal and external environment by an individual that feels under threat (physically, cognitively and emotionally). The scrutiny and evaluation of internally and externally generated *inputs* is central to the formulation of decisions relating to *output* generation and the choice of behaviours relating to the threat of low back pain.

The OFC is involved in multiple roles in sensory integration, reward processing, decision making and hedonic processing (Kringelbach 2005). The OFC is involved in appraising the valence and reward value of multi-sensory stimuli (O'Doherty 2004) and, in conjunction with the amygdala and ventral striatum, reward prediction, allowing behaviour to be organised in advance of stimuli. In particular, activity in the medial OFC is thought to encode the reward value of reinforcers, whereas activity in the

lateral OFC is thought to encode the reward value of punishers, leading to changes in behaviour. Ultimately, the OFC has a key role in the decision-making process itself (Bechara, Damasio et al. 2000, Bechara, Tranel et al. 2000). Patients with orbitofrontal lesions are impaired in everyday decision-making despite normal intellectual capacity (Bechara, Damasio et al. 2000, Kringelbach 2005).

Our behavioural data provide ample evidence of the impact of CLBP and, in particular, NuLBP, on the quality of life of this cohort of patients; a finding consistent with a wide variety of pain related and psychometric domains. In particular, GM alterations in the OFC and insula cortex may particularly reflect the reduced decision-making capacity and consequent behavioural choices of CLBP patients with neuropathic, compared to non-neuropathic symptoms. It would be of particular interest in future to examine variability in these regions using BOLD fMRI in these diagnostic groups in tasks designed to probe decision-making processes.

4.6.2.2 **DLPFC GM Reductions In CLBP And NuLBP Patients May Reflect Deficits In Decision-Making**

We also observed reductions in DLPFC GM volume in NuLBP compared to MLBP subjects and in CLBP subjects compared to controls.

The DLPFC is involved in many higher-level cognitive processes, collectively termed executive function, including working memory, attention, set-shifting, reward evaluation and motor planning (Schmitz, Kawahara-Baccus et al. 2004, Murray and Ranganath 2007, Ardila 2008).

CLBP patients with altered levels of DLPFC metabolites and decreased GM volume perform poorly in tests designed to test “emotional decision making” (Iowa Gambling Task) and executive function (Grachev, Fredrickson et al. 2000, Apkarian, Sosa et al. 2004, Apkarian, Sosa et al. 2004). I therefore suggest that the reductions in DLPFC GM volume we have observed may help to explain the cognitive deficits experienced by many CLBP and chronic pain patients (Keogh, Moore et al. 2013). Chronic pain patients frequently complain of cognitive deficits, such as reduced ability to concentrate when reading or watching a film, or of poor routine task performance. Clinicians may be inclined to dismiss such comments as irrelevant to the clinical picture of the patient. However, I suggest that the OFC reductions we have observed in NuLBP patients compared to controls, and DLPFC GM reductions in both groups, are linked to poor decision-making and subsequent maladaptive behavioural choices observed in CLBP patients.

Both these areas are reduced significantly in NuLBP compared to MLBP patients and CLBP compared to controls. In particular, the DLPFC appears to be involved in evaluating long term versus short-term gain, via high level ‘neuroeconomic’ processing (Glimcher 2013) whereas by contrast, the OFC is involved with assessing the immediate reward value of a sensory stimulus (Kringelbach, de Araujo et al. 2004, Kringelbach 2005). This suggests that higher order DLPFC processing inhibits immediate reward gratification. Local reductions in GM in these regions may reflect regulatory dysfunction between the OFC and DLPFC and also

reflect the greater behavioural costs of neuropathic back pain, as demonstrated in our behavioural data. Such behavioural sequelae are seen clinically in maladaptive cognitions and behavioural patterns, such as under and over activity, withdrawal from usual activities of daily living, social withdrawal, over-reliance on prescription and non-prescription medication, over-reliance on seeking treatments in spite of lack of success, negative appraisal, rumination and catastrophising.

4.6.2.3 GM Reductions In NuLBP Patients Compared To MLBP In The ACC/OFC/Insula, May Reflect Increased Attentional Resources Devoted To Monitoring The Internal Environment And Stimulus Saliency.

In NuLBP, compared to MLBP patients, we observed GM reductions in the anterior division of the mid cingulate and orbitofrontal insula. We also observed changes in the pregenual ACC in CLBP patients compared to controls. GM reductions in the cingulate/OFC /anterior insula may reflect perturbations in assessment of the salience of internally generated stimuli, resulting in in terms of their potential threat/reward value. I speculate that such alterations may play a role in altered decision-making processes observed in patients with CLBP.

The anterior insula, in conjunction with the ACC and OFC, has been previously suggested as a site for integration of pain perception (Brooks and Tracey 2005), coding of pain intensity (Coghill, Sang et al. 1999) and where multimodal stimuli from the body, including pain) are estimated/surveyed (interoception) (Craig 2003) in order to evaluate the

state of the body and assess the need to take action, in order to maintain homeostasis. Moyaedi and Weissman-Fogel, however, (Moayedi and Weissman-Fogel 2009), citing the work of Moraux and Iannetti (Mouraux, Diukova et al. 2011) point out that it is as yet unknown whether the insula codes primarily for pain, rather than for stimulus saliency. The anterior insula and ACC have been posited as forming the core of a salience network that governs processing of hierarchical behavioural responses to stimuli including accessing attentional or working memory networks and coordinating autonomic and motor responses, as well as modulating contextual emotional and sensory inputs with other subcortical and cortical areas (Flor, Knost et al. 1997, Seeley, Menon et al. 2007, Menon and Uddin 2010). The anterior insula has also been implicated in Damasio's "somatic marker" hypothesis in processing somatic and visceral input, in order to frame an emotional response on which decision-making is predicated (Damasio, Grabowski et al. 2000, Damasio 2005). I suggest that reductions in these areas reflect the dysregulation of emotional control in decision-making that is seen clinically in CLBP patients whereby exaggerated emotional responses are associated with somatic markers such as the alterations in physiological behavioural responses (alterations in muscle tone/guarding, alterations in movement patterns) that are associated with an emotional response (e.g. fear/anxiety) in response to a behavioural challenge (e.g. walking, sitting to standing, lifting). Over time, the behavioural and corresponding emotional responses may become conditioned.

Furthermore, Changes in OFC/insula were seen primarily in the NuLBP population. I further speculate this finding may reflect the increased affect on salience of neuropathic pain due to increases in pain intensity, impact on quality of life and increased negative affect observed in our behavioural data; a reflection of the attentional resources increasingly devoted to maladaptive assessment and vigilance towards the ongoing nature of their pain by the NuLBP population.

Our study also identified GM alterations in additional regions of the salience network in both NuLBP subjects (cingulate, anterior insula, DLPFC, cerebellum and precuneus) and in CLBP subjects (anterior cingulate, prefrontal cortex including the DLPFC and MFPC, hippocampus, parietal lobe, basal ganglia, precuneus, brainstem and temporal gyrus) (for a review of key areas associated with salience networks and pain see (Borsook, Edwards et al. 2013)). GM reductions in these regions may underpin heightened states of alertness and responsiveness to both painful and non-painful stimuli that are seen clinically in patients with CLBP; especially in NuLBP patients, who demonstrate higher levels of pain with greater negative affect as described in the previous chapter.

Widespread dysregulation in sensory processing and lowering of thresholds for stimulus saliency that occurs in CLBP may be linked to the GM alterations and dysregulation seen in regions of salience networks in this study. For instance, CLBP patients describe sour taste stimuli as significantly more intense than normal controls (Small and Apkarian

2006) and are less able to disregard incoming auditory information (Fann, Preston et al. 2005). CLBP patients also demonstrate an enhanced EEG signal to pain-related words (Flor, Knost et al. 1997) and report increased pain when viewing images of painful events. It has been shown that the increased pain levels are associated with activation in the precuneus, cingulate and anterior insula, part of the salience network (Shimo, Ueno et al. 2011). Similar results are described for migraine sufferers reporting increased symptoms on viewing pain-related words (Eck, Richter et al. 2011). Practical constraints limited the amount and spread of neuropsychological testing of our participants, but future studies should include more generalised assessment of stimulus saliency in individuals with CLBP. Such testing would facilitate understanding of potential relationships between stimulus saliency, local variability in GM and its interaction with clinical back phenotypes.

4.6.2.4 GM Increases In The Basal Ganglia In CLBP Patients Compared To Controls: Might These Changes Relate To Increasing Demands Of Integrating Cortical And Sub-Cortical Networks Involved In Pain Processing?

In CLBP subjects compared to controls, largely driven by the MLBP group, we observed bilateral increases in the lentiform nuclei (incorporating medial and lateral globus pallidus and putamen) extending into the nucleus accumbens. I suggest that these GM increases are related to the involvement of the basal ganglia in integrating and modulating sensory, cognitive and affective elements of the pain experience via cortical and sub-cortical feedforward and feedback loops,

which incorporate multiple inputs from areas where we have also seen GM alterations (DLPFC, ACC, hippocampus, orbitofrontal, pre-motor, M 1, S1 and parietal cortex) (Chudler and Dong 1995, Schweinhardt, Kuchinad et al. 2008, Borsook, Upadhyay et al. 2010). Furthermore, the nucleus accumbens (NAc), part of the dopaminergic mesolimbic pathway, encodes valuation of reward or punishment value ascribed to actions (O'Doherty 2004, Montague, King-Casas et al. 2006, Schultz 2006). Reports of functional connectivity analysis of resting-state fMRI data, using NAc as a seed, have reported inter-relationships between the NAc and brain areas where we have seen GM alterations associated with valuation, action selection and pain modulation such as the basal ganglia, amygdala, ACC, MPFC, OFC, thalamus and anterior insula. (Baliki, Geha et al. 2010).

I therefore propose that the bilateral basal ganglia GM increases we have observed in CLBP patients (and that others have observed in CLBP (Schmidt-Wilcke, Leinisch et al. 2006) and in other clinical conditions (Schmidt-Wilcke, Luerding et al. 2007, Schweinhardt, Kuchinad et al. 2008) reflect the on-going assessment of the threat and reward value of intended and actual behavioural decisions that have to be taken on a moment to moment basis, when actions and activities are no longer pain-free and thoughtless due to LBP. A suitable BOLD (blood oxygen level dependent) fMRI decision-making experiment in individuals with CLBP and indeed other persistent pain phenotypes would prove to be an exciting avenue for future research to test such a working hypothesis.

4.6.2.5 GM Increases In CLBP Patients Compared To Controls In The Basal Ganglia Relate To Planning Motor Strategies And Adjusting To Altered Movement And Muscle Activation Patterns.

The increased basal ganglia GM volume that we have observed may equally be an adaptive response to increased afferent and/or aberrant inputs, or may result from abnormalities in dopaminergic regulation due a combination of aberrant inputs and increased computational workload. Basal ganglia GM increases were identified in CLBP patients compared to controls and in MLBP (but not NuLBP) subjects compared to controls, which suggests that the increases reflect a population that are still actively involved in planning motor strategies (and concurrently adjusting to altered movement and muscle activation patterns frequently identified in CLBP populations (Hodges and Richardson 1999, Hodges, Moseley et al. 2003, Ferreira, Ferreira et al. 2004, MacDonald, Moseley et al. 2006, MacDonald, Moseley et al. 2009, Hodges and Tucker 2011). In addition, it is interesting to note that the GM increases and decreases we observed in the motor cortex were also seen in MLBP (and not NuLBP) subjects compared to controls. We observed GM increases in right premotor, M1 and S1 areas that correspond to the homuncular representation of the trunk. However, we also saw GM reductions in left S1 and M1 regions that were more inferiorly located and extended into the parietal operculum (S2). These increases are therefore more likely associated with the integration of sensory (including proprioceptive and pain stimuli) and motor stimuli to coordinate motor activity (Proske and Gandevia 2009, Eickhoff, Jbabdi et al. 2010) which, I suggest, provides evidence in

support of a theory of individuals with LBP actively utilising motor strategies via feedforward and feedback loops between primary and secondary motor regions and the basal ganglia, to manage ongoing CLBP. Furthermore, the fact that these changes relate to the MLBP population may be related to increased dysregulation in sensory-discriminative networks in the NuLBP population. Normal sensory-discriminative processes will allow a measured and appropriate motor response to stimuli. I suggest that mechanical back pain retains its association with movement provocation and works to adopt appropriate motor strategies. However, neuropathic pain is characterised by a non-linear response to stimuli – pain out of proportion to the stimulus, latency, unusual pain perception – that may make an appropriate behavioural motor response challenging due to altered input mechanisms.

One may also further speculate that the reason these increases are not seen in the NuLBP subjects is that the NuLBP population is directing ever-increasing resources towards vigilance and prevention of pain by *reducing* activity (as evidenced by our behavioural data) and less towards planning motor strategies to *actively* deal with ongoing back pain. I suggest that these results indicate that CLBP patients demonstrate a continuum, in which initial resources are directed at developing motor strategies, which, as the impact of CLBP increases, are either exhausted or extinguished. Therefore, the basal ganglia and motor cortex may be a key indicator (in some patients) of the transition from mechanical to neuropathic back pain. This is further evidence that mechanical and

neuropathic back pain may not depend as much on peripheral mechanisms as is widely believed but may rather be mediated by supraspinal mechanisms in the central nervous system. Admittedly such theories are highly speculative and ultimately are only testable within longitudinal study frameworks, for example, ‘at risk’ studies where individuals may be followed from their early acute presentations of episodes of back pain.

4.6.2.6 **Fear Avoidance In CLBP May Be Related To GM Alterations And Dysregulation Of Pain Saliency Networks.**

Knowledge of GM alterations in areas involved in saliency, executive function and motor planning, may force clinicians to reconsider long held beliefs about patients with CLBP. For instance, the somewhat pejorative term “fear avoidance”, used to describe the phenomenon in which patients with CLBP avoid activities or situations that trigger pain, may be less to do with psychological concepts of fear (and the implication that these patients are somehow cowardly and weak) and more to do with alterations and dysfunction in networks devoted to salience, executive function and motor planning. I suggest that fear avoidance is more to do with dysregulation in these networks, leading to increased vigilance towards, and on-going assessment of, stimuli related to persistent low back pain. Furthermore, failures in neuroeconomic decision making when faced with choices of action and inaction, linked to short-term gains (pain reduction) versus long-term benefits (participation in an active lifestyle), result in poor behavioural choices. Patients have the intellectual capacity to understand that excessive reduction in activity levels is harmful,

causing not only increased disability but paradoxically, increased pain intensity (Vlaeyen and Linton 2000, Leeuw, Goossens et al. 2007). These data, however, suggest that GM alterations in salience, executive function and motor planning networks may perturb the ability of CLBP patients to optimally evaluate sensorimotor stimuli and predict rewards and outcomes of normative functioning in their everyday lives.

4.6.2.7 **GM Alterations In The Mid Cingulate Cortex In NuLBP Patients Compared To MLBP Relate To Ongoing Behavioural Evaluation And Motivational Decision-Making Strategies Associated With NuLBP.**

We witnessed GM reductions in the anterior (aMCC) and posterior (pMCC) mid cingulate in NuLBP compared to MLBP patients (and in pregenual ACC / MPFC (medial prefrontal cortex) in CLBP patients, compared to controls).

I suggest that GM alterations in the mid cingulate provide further evidence of perturbed ongoing behavioural evaluation and motivational decision-making strategies associated, in particular, with NuLBP. A key role of the cingulate is to integrate pain, cognitions and emotions in order to ensure appropriate behavioural responses to pain and to coordinate pre-motor planning and skeletomotor orientation (Vogt 2005, Shackman, Salomons et al. 2011). Not all parts of the cingulate are equally involved in emotion, and studies suggest discrete parcellation of emotional processing (Vogt 2005) The anterior MCC, in particular, is associated with fear (Vogt and Pandya 1987) due to its cortical connections with the

amygdala. In contrast, the pMCC is not associated with emotional processing but is involved with skeletomotor orientation in response to noxious stimulation (Vogt 2005). Shackman suggests the dorsal aspect of the anterior MCC is a hub where negative affect, pain and cognitive control overlap to direct goal-orientated behaviour, especially when outcomes are uncertain (Shackman, Salomons et al. 2011) (such as when a patient with CLBP is engaged in a difficult and painful functional task). As a result, increased anterior MCC activity is observed (along with other higher order centres, such as the DLPC) in individuals with high levels of fear avoidance (Vogt 2005, Shackman, Salomons et al. 2011). I suggest that GM alterations in the aMCC and pMCC in NuLBP patients may be a neuroplastic response to the emotional cost of on-going neuroeconomic decision making associated with CLBP and skeletomotor planning associated with behavioural responses. In future studies dedicated neuropsychological assessment of decision-making processes, in concert with structural MRI image analysis techniques, should be employed to better understand such potential relationships.

4.6.3 **Pain Affect**

We observed significant GM alterations in the DLPFC, orbitofrontal cortex, hippocampus, basal ganglia and ACC in CLBP and, in NuLBP, patients compared to controls. These areas, have previously been associated with processing the affective components of the pain experience and are also implicated in low mood and depression (Drevets 2007, Egger, Schocke et al. 2008, Vasic, Walter et al. 2008, Cole,

Costafreda et al. 2011, Hamilton, Etkin et al. 2012, Grieve, Korgaonkar et al. 2013).

The observed GM alterations suggest not only evidence of the neural correlates of the high cost of suffering experienced by CLBP patients (as evidenced by our behavioural data) but also possible dysfunction and dysregulation of mood, further augmenting the emotional content of CLBP. GM alterations in these areas may be an adaptive response to living with CLBP. However, dysregulation in these areas may equally heighten the emotional aspects of living with chronic pain in CLBP patients and in particular, in our NuLBP patients; a view, which is reflected in our behavioural data.

The ACC is consistently implicated in functional pain imaging studies as a key area for processing the affective-motivational components of pain (Treede, Kenshalo et al. 1999, Vogt 2005, Etkin, Egner et al. 2011). In particular, the pregenual ACC mediates the feeling of unpleasantness in pain sensation (Hofbauer, Rainville et al. 2001, Vogt 2005). It is active during persistence of negative affect and in particular, during reflection on negative emotional states (Northoff, Richter et al. 2000, Schweinhardt and Bushnell 2010) and in detection of unfavourable outcomes (Ridderinkhof, Ullsperger et al. 2004). Studies have shown GM reductions in the ACC in numerous pain states (hip osteoarthritis (Rodriguez-Raecke, Niemeier et al. 2009), headache (Rocca, Ceccarelli et al. 2006), idiopathic facial pain (Schmidt-Wilcke, Hierlmeier et al. 2010) and also in LBP patients with Ankylosing Spondylitis (Wu, Inman et al. 2013).

GM reductions in the pregenual ACC associated with processing pain unpleasantness may reflect the fundamental evolutionary importance of negative affect in the experience of pain. If ultimately the purpose of pain is motivational – to serve as a warning, a threat signalling danger, requiring action to prevent further harm, either by retreat away from an outside threat or, in the case of injury to the body, rest and recovery, then the *unpleasantness* of pain is key to motivating the individual to take action (Robinson and Riley III 1999). Pain without emotion lacks saliency and negative emotions in response to pain promote vigilance. Pain is a vital component of learning, enabling the individual to avoid future harm. Without emotional saliency, learning cannot take place. It is suggested that individuals with congenital insensitivity to pain are unable to learn from painful experiences, not because they do not experience the sensory-discriminative aspects of pain, but because their pain lacks emotional valence (Minde, Svensson et al. 2006). Consequently, these individuals do not develop protective responses to aversive stimuli and therefore suffer repeated injury with potentially fatal consequences.

4.6.3.1 **Low Mood Is Associated With CLBP**

I suggest that in addition to its role in sensorimotor evaluation and motor planning, the GM increases we have identified in CLBP subjects compared to controls may be associated with the incidence of low mood in our CLBP population. Reduction of dopaminergic activity in the mesolimbic pathway has been linked to depression and anhedonia (Nestler and Carlezon 2006, Nutt, Demyttenaere et al. 2007, Van den

Heuvel and Pasterkamp 2008, Tye, Mirzabekov et al. 2013). Furthermore, GM alterations may cause, or else be a consequence of dysregulation of functional connectivity between the nucleus accumbens and the ACC, leading to errors in affective pain processing (Baleydier and Mauguiere 1980). The alterations in these areas may reflect the low mood and exaggerated emotional responses seen clinically in patients with CLBP and demonstrated by both our behavioural data and also the work of others (Sullivan, Reesor et al. 1992, Bair, Robinson et al. 2003, Currie and Wang 2004, Katona, Peveler et al. 2005, Linton 2011, Walker, Kavelaars et al. 2014). In this thesis regression analyses between psychometric variables and GM integrity were not attempted, but such additional investigations may provide insights into the relationship between morphometric and affective changes observed in individuals with CLBP.

4.6.4 **Pain Modulation**

We observed alterations in GM in the ACC/MPFC, DLPFC, S1 and basal ganglia in CLBP patients compared to controls and also in the mid cingulate, OFC and DLPFC in NuLBP patients compared to MLBP.

These areas are involved in multi-modal roles in pain processing, encompassing modulation (Tracey 2010), threat evaluation, cognitions, mood, emotions and behavioural decision-making. GM alterations in these areas may indicate a maladaptive response to on-going pain and low mood and a reduced capacity for both placebo and non-placebo endogenous pain modulation via cortico-subcortical and cortico-cortical pathways.

Throughout this thesis I consider pain to be an amalgam of sensory-discriminative, affective-motivational and cognitive-evaluative processes (Melzack and Casey 1968, Mollet and Harrison 2006, Wiech and Tracey 2013). The GM reductions we have observed in frontal cortical areas are evidence of shared affective-motivational, cognitive-evaluative and sensory discrimination networks (NuLBP: DLPFC, orbitofrontal cortex, mid cingulate, insula; MLBP: DLPFC, hippocampus, basal ganglia, and pACC/MPFC, S1, insula). My findings are consistent with those of others (Bushnell, Kuchinad et al. 2007, Bingel and Tracey 2008, May 2008, Apkarian, Baliki et al. 2009, Henry, Chiodo et al. 2011, May 2011). These areas are frequently associated with pain intensity modulation (placebo

and non-placebo) mediated by emotions and mood, cognitions, expectation and context.

4.6.4.1 GM Volume Reductions We Observed In The Cingulate Cortex In CLBP Patients Compared To Controls And Also NuLBP Patients Compared To MLBP Are Evidence Of Dysregulation In Pain Modulation.

We identified significant bilateral anterior mid cingulate reductions in NuLBP patients and pregenual ACC and left MPFC volume in CLBP patients compared to controls. These areas have been implicated previously in processing of negative affect (Vogt 2005). GM changes in these regions may be associated with the modulation of ongoing pain, in conjunction with prefrontal and sub cortical networks. Supraspinal dysregulation of pain modulation has been suggested as a major reason for persistent clinical pain especially in the absence of, or out of proportion to, identifiable pathology, as is frequently seen in CLBP (Apkarian, Baliki et al. 2009, Tracey and Bushnell 2009, Apkarian 2011). The pregenual and subgenual rostral ACC (and also other areas in which we have shown GM alterations such as DLPFC, insula and nucleus accumbens) are crucially involved in pain modulation in both opioid and placebo analgesia (Petrovic, Kalso et al. 2002, Wager, Scott et al. 2007) and non-placebo modulation effects, such as in distraction (Bantick, Wise et al. 2002, Tracey, Ploghaus et al. 2002). Alterations in GM in these areas may reflect disrupted pain modulatory mechanisms, resulting in increased pain perception relative to stimulus intensity and increased duration of pain post-stimulus. These are frequently seen clinically and

unfortunately are often termed “exaggerated illness behaviours “ that are linked to a non-organic (i.e. made-up) presentation. In fact, tests have even been designed to catch-out patients with an increased pain presentation who are “faking” their symptoms (Waddell, McCulloch et al. 1980, Blom, Taylor et al. 2002). Waddell’s signs are a series of tests designed to identify psychosomatic symptoms in CLBP patients. While Waddell’s signs may be an indicator of significant psychological distress, any suggestion they may be used to detect malingering patients is evidence of a misunderstanding of the mechanisms that underlie many, if not the majority, of chronic pain states and must be vigorously challenged. I suggest that the GM alterations in modulatory networks that this study has identified in the ACC and other areas provide evidence of dysfunctional inhibitory mechanisms that underlie the clinical manifestation and persistence of CLBP other clinical pain states and the failure of pharmacological, surgical and conservative treatment regimes that occur in the majority of CLBP patients.

4.6.4.2 GM Volume Reductions We Observed In The Orbitofrontal Cortex In NuLBP Patients Compared To MLBP Are Associated With Alterations in Pain Modulation.

We observed reductions in other areas associated with modulation of pain. I suggest that the reductions in the OFC GM that we observed in NuLBP compared to MLBP subjects, are associated with the increases in pain scores reported by our NuLBP patients. Reduced cortical thickness in the OFC (as well as mid cingulate and S1) is associated with reduced heat pain thresholds (Erpelding, Moayedi et al. 2012) and co-activation of

the OFC and ACC is observed in subjects that respond to placebo (Petrovic, Kalso et al. 2002). Furthermore, GM alterations related to the salience network that we observed in NuLBP patients (in particular, the ACC, OFC and anterior insula) have been linked to deficits in habituation to tonic pain stimuli seen in chronic pain patients (Seeley, Menon et al. 2007). Reductions in OFC GM may reflect a failure of endogenous pain regulation in NuLBP cohort.

4.6.4.3 **GM Volume Alterations We Observed In S1 In CLBP Patients Compared To Controls May Relate To Reductions In Pain Thresholds.**

We observed a significant reduction in GM volumes in the S1 cortex. The S1 cortex may be involved in not only perception but also modulation of both painful and non-painful somatosensory sensation, although this has been the subject of some debate (Bushnell, Duncan et al. 1999). Recently, S1 reductions in cortical thickness have been shown to correlate with reductions in thresholds to pain sensitivity (Emerson, Zeidan et al. 2013). The GM reductions in the trunk area of S1 may also therefore be associated with dysregulation of pain modulation as well as with changes to cortical representation and is consistent with the implications of our behavioural data.

4.6.4.4 GM Volume Reductions We Observed In The DLPFC In CLBP Patients Compared To Controls And Also In NuLBP Patients Compared To MLBP Are Likely To Reflect Reductions In Inhibitory Pain Modulation.

We found bilateral GM DLPFC reductions in CLBP subjects compared to controls and unilateral reductions in DLPFC GM in NuLBP patients compared to MLBP. The incidence of DLPFC GM reductions reported in the literature in CLBP studies is witness to the important role of the DLPFC in pain regulation (Apkarian, Sosa et al. 2004, Schmidt-Wilcke, Leinisch et al. 2006, Seminowicz, Wideman et al. 2011, Ivo, Nicklas et al. 2013). Importantly, CLBP patients, whose symptoms improved after treatment, were shown to have normalization of DLPFC GM thickness (Seminowicz, Wideman et al. 2011). The DLPFC plays a key role in pain modulation via “top-down” cortical and subcortical pathways (Grachev, Fredrickson et al. 2002, Grachev, Ramachandran et al. 2003, Lorenz, Minoshima et al. 2003, Zubieta 2003, Giesecke, Gracely et al. 2004, Wager, Rilling et al. 2004, Schmahl, Bohus et al. 2006, Zubieta, Yau et al. 2006, Fierro, De Tommaso et al. 2010, Krummenacher, Candia et al. 2010).

4.6.4.5 GM Volume Increases In The Brainstem May Relate To Compensatory Mechanism For GM Reductions In The DLPFC

As well as DLPFC reductions, we also showed GM increases in the brainstem (*from the upper medulla to the mid section of the pons)* in CLBP subjects and, exclusively in NuLBP subjects compared to controls.

DLPFC mediated placebo is linked to activity in the periaqueductal grey matter in the brainstem (Wager, Rilling et al. 2004). A possible reason therefore, for GM volume increases in the brainstem may relate to compensatory mechanism for GM reductions in the DLPFC.

GM reductions in the DLPFC in CLBP subjects compared to controls and also in NuLBP patients compared to MLBP may reflect dysregulation of inhibitory mechanisms on the MPFC.

Similarly, the additional GM reductions we observed in CLBP subjects compared to controls in the MPFC may relate to top down dysregulation of MPFC activity by the DLPFC, which has been shown to negatively correlate with pain intensity (Lorenz, Minoshima et al. 2003, Baliki, Chialvo et al. 2006, Schmahl, Bohus et al. 2006) and appears to have an inverse relationship with the MPFC in spontaneous clinical pain (Baliki, Chialvo et al. 2006).

GM volume reductions we observed in the DLPFC in CLBP patients compared to controls and also in NuLBP patients compared to MLBP may play a role in the maintenance and persistence of enhanced pain affect in addition to pain intensity.

In addition, GM DLPFC reductions are implicated not only in the dysregulation of pain modulation but also of pain affect (Lorenz, Minoshima et al. 2003, Seminowicz and Davis 2006). Therefore, I suggest that the GM reductions we have observed in the DLPFC may

reflect a reduced ability of “top down” regulation on cortical centres regulating pain affect, resulting in the increased levels of pain intensity and of negative affect seen in CLBP patients and, in particular, the NuLBP population. A probable mechanism is failure of top down DLPFC regulation of the rACC and insula, both areas in which we have observed GM reductions in both CLBP patients compared to controls and NuLBP compared to MLBP patients. Low levels of DLPFC activity are associated with increased pain intensity and unpleasantness, which correspond with rACC (rostral anterior cingulate cortex) and anterior insular activity (Lorenz, Minoshima et al. 2003). Activity in the DLPFC is also reduced in distressed compared to less distressed axial CLBP patients (Lloyd, Findlay et al. 2008). Therefore, GM DLPFC reductions may play an important role in the maintenance and intensification of pain affect as well as pain intensity. Furthermore, GM increases in the thalamus in CLBP patients reflect dysregulation in pain processing networks.

We observed GM increase in the lentiform nucleus, which extended into the margin of the right thalamus when comparing CLBP subjects with controls. Although GM alterations in the thalamus did not achieve statistical significance when comparing NULBP and MLBP groups, we saw GM increase in the right thalamus uniquely in NuLBP subjects when individually comparing LBP sub-groups to controls.

The thalamus is one of the most frequently observed areas in experimental pain studies and is thought to be involved primarily in the sensory-discriminative aspects of pain processing, although it may also

be associated with general arousal patterns in relation to pain (Peyron, Laurent et al. 2000). The GM increase that we observed may therefore simply relate to ongoing nociceptive processing. However, there is evidence that the thalamus and brainstem comprise a pain modulatory network (Valet, Sprenger et al. 2004), and therefore GM thalamic increase may either be seen as an adaptive mechanism in pain modulation, to manage increased levels of nociception or conversely, representing maladaptive dysregulation of inhibitory modulation, resulting in the increased pain levels and temporal and spatial spontaneity of neuropathic pain. In fact, a substantial body of evidence points to the involvement of the thalamus in neuropathic pain both in animal (Paulson, Morrow et al. 2000, Paulson, Casey et al. 2002) and human models (Baron, Baron et al. 1999, Casey, Morrow et al. 2001, Casey, Lorenz et al. 2003, Lorenz and Casey 2005, Yen and Lu 2013). The thalamic GM increases we have seen may therefore instead point to the widespread dysregulation in sensory processing, hypersensitivity and non-dermatomal pain patterns that are seen in neuropathic pain.

4.6.5 **Body Image**

4.6.5.1 **GM Alterations In The Pre-Central And Post-Central Gyri Relate To Alterations In Sensory Processing In CLBP Patients Compared To Controls.**

We observed both increases and reductions in GM volume in separate regions of both pre-central and post-central gyri. GM increases were seen in right premotor, M1 and S1 areas that correspond to the homuncular

representation of the trunk. Patients with CLBP experience abnormal motor function and altered movement patterns, proprioceptive deficits and changes to body awareness and perception. The clinical examination data shows evidence of altered sensory processing of two-point and tactile threshold discrimination. There is substantial evidence that these changes are linked to functional and structural changes in representational maps in the motor (M1) and sensory (S1) cortex (Wand, Parkitny et al. 2011). I suggest that the GM increases in right premotor, M1 and S1 areas are evidence of cortical reorganisation in our CLBP cohort and that these changes are also relevant to not only pain intensity and motor function but even to concepts of self-image and bodily identity and further support our examination data.

Generally, CLBP studies have shown reductions in GM volume or cortical thickness in the post-central gyrus (S1) (Apkarian, Sosa et al. 2004, Schmidt-Wilcke, Leinisch et al. 2006, Ivo, Nicklas et al. 2013, Wu, Inman et al. 2013) although one study has shown increased cortical thickness bilaterally in S1 (Kong, Spaeth et al. 2013). In a multivariate analysis employing a machine learning approach with Support Vector Machines (SVM) to identify areas of structural alteration that can be used to classify LBP, increases were also found in S1 and S2 although care must be taken in extrapolating results obtained by this different methodology (Ung, Brown et al. 2012). Surprisingly, given that patients with LBP demonstrate profound alterations in activity levels, movement patterns and muscle activation, there is a paucity of data available, I have been able to identify

only one study showing GM alterations in M1 (Ivo, Nicklas et al. 2013). This may be in part explained by methodological difficulties; differentiating S1 from M1 in spatially smooth data remains a technical challenge for VBM methodologies and cortical flattening techniques may be a suitable technology to assess issues of sensory-motor disambiguation (Fischl, Sereno et al. 1999).

Normal body schemas are dependent on both regular somatosensory and proprioceptive input and motor output. In CRPS and PLP, altered afferent input, both painful and non-painful, is linked to disruption of motor (M1) and sensory (S1) cortical representational maps (Moseley and Flor 2012). Similar disruption of cortical representational maps are seen in CLBP using MEG (Flor, Braun et al. 1997) and fMRI (Lloyd, Findlay et al. 2008). Both studies show a medial shift in the representation of the back in the somatosensory cortex. Changes in body schema are associated with alterations in sensory function, in particular to tactile acuity (two point discrimination) and also pain intensity and are consistent with the examination and behavioural data from the cohort of patients in this thesis. This supports the findings of other groups who have demonstrated similar alterations in CRPS and PLP (Maihofner, Handwerker et al. 2003, Pleger, Tegenthoff et al. 2004, Maihofner, Forster et al. 2005) and also in CLBP (Wand, Di Pietro et al. 2010, Luomajoki and Moseley 2011).

Proprioceptive deficits and motor control disorders in patients with CRPS and PLP are also associated with altered cortical representation (Anderson-Barnes, McAuliffe et al. 2009, van Rijn, van Hilten et al. 2009).

Deficits in motor control, muscle activation and poor proprioceptive acuity of the lumbo-pelvic region in CLBP patients also show a close association with increased 2PD thresholds on the back (for a review see (Hodges and Moseley 2003)) and changes to M1 representational maps (Tsao, Galea et al. 2008, Tsao, Danneels et al. 2011, Wand, Parkitny et al. 2011).

I suggest that our clinical examination data, which shows evidence of alterations in two-point sensory discrimination thresholds and tactile threshold deficits, together with the GM alterations in motor and sensory representational areas we have demonstrated, provides evidence of changes in S1 and M1 body schema in CLBP. Furthermore, I suggest that our data are further evidence of shared neural mechanisms underlying CLBP and other conditions such as PLP and CRPS. Our data show the neural correlates of deficits in motor control, muscle activation and proprioception that have been reported by other LBP studies (Flor 2003, Hodges and Moseley 2003, Wand and O'Connell 2008, Wand, Di Pietro et al. 2010, Luomajoki and Moseley 2011, Wand, Parkitny et al. 2011). Such theories set the stage for future studies with convergent methodologies incorporating not only examination of brain structure, resting-state brain function and basic clinical and psychometric investigations, but hypothesis-driven investigation of body schemas, for example using BOLD fMRI and electrophysiological techniques such as EEG and MEG.

4.7 Conclusions

4.7.1 Brain Morphometry And NuLBP

To the best of my knowledge, this is the first study to directly investigate the structural correlates of neuropathic and non-neuropathic CLBP and to directly compare and contrast between neuropathic and non-neuropathic CLBP groups. We have been able to demonstrate GM reductions in the OFC, anterior insula, mid cingulate, DLPFC and cerebellum and GM increases in the precuneus in NuLBP patients compared to MLBP.

Prior to this current study, no studies attempted to investigate whether it was possible to identify a discrete morphometric neural signature for neuropathic low back pain. This is therefore the first study to show clearly identifiable structural differences in clearly characterised neuropathic and non-neuropathic CLBP patient groups. Although there have been numerous studies investigating the structural components of CLBP (Apkarian, Sosa et al. 2004, Schmidt-Wilcke, Leinisch et al. 2006, Buckalew, Haut et al. 2008, Seminowicz, Wideman et al. 2011, Ivo, Nicklas et al. 2013, Kong, Spaeth et al. 2013, Wu, Inman et al. 2013), comparison of morphometry across CLBP studies is problematic due to the wide variations in patient selection criteria, methodologies and results (as discussed previously), which we have attempted to overcome by better phenotyping methods. In particular, only two studies attempted to characterise patients groups into neuropathic and non-neuropathic sub-groups (Apkarian, Sosa et al. 2004, Wu, Inman et al. 2013). Davis' group

had some similar areas of GM volume reductions (primary somatosensory cortex, insula, anterior mid-cingulate cortex and anterior cingulate cortex) and increases (putamen and thalamus) to our study (Wu, Inman et al. 2013). Unfortunately, further comparisons are problematic as they chose a CLBP group with a specific pathology Ankylosing Spondilitis (AS) and used cortical thickness analysis to measure volume, rather than VBM. Apkarian's study showed decreased GM density in the DLPFC and thalamus. Reductions in density in the DLPFC but not in the thalamus were greater in the neuropathic cohort compared to the non-neuropathic subjects. (Apkarian, Sosa et al. 2004). However, neither study compared and contrasted neuropathic and non-neuropathic patient groups which is central to this thesis.

4.7.2 **Future Directions**

Different neuropathic clinical conditions and different neuropathic pain symptoms appear to involve different neural mechanisms (Ducreux, Attal et al. 2006, Youssef, Gustin et al. 2014). Structural neuroimaging studies show GM alterations specific to each individual clinical condition (May 2011, Smallwood, Laird et al. 2013). Further studies need to be undertaken to identify the neural correlates of differing neuropathic clinical presentations either by clinical diagnosis (i.e. neuralgia compared to neuropathy) or by symptoms (i.e. conditions characterised predominantly by spontaneous pain compared to conditions characterised by mechanically evoked pain). For instance, another study

could examine different neural correlates of NuLBP with clinical identifiable neuropathy compared to NuLBP with neuralgia alone.

4.8 **Final Conclusion**

Reviews of chronic pain neuroimaging (Tracey and Bushnell 2009, Henry, Chiodo et al. 2011, Lee and Tracey 2013) have described a distinct neural signature associated with chronic pain, which does not primarily engage brain areas involved with sensory discrimination but rather areas associated with affective and cognitive processing – the so-called "emotional brain" (Baliki, Chialvo et al. 2006).

This study has demonstrated significant GM volume alterations in patients with CLBP compared to controls. CLBP patients show changes in areas associated in particular with cognitive-evaluative and affective-motivational processing related to pain modulation and behavioural decision-making. I also suggest that taken as a whole, these areas represent a neural correlate for feelings of loss of body identity and awareness. I have also shown significant GM volume alterations in patients with CLBP that differ due to underlying clinical phenotypes; NuLBP subjects show distinct GM volume reductions in areas associated with interoception, evaluation of environment and stimulus saliency and neuroeconomic processing of behavioural choices, reflecting the increasing cognitive–evaluative and affective-motivational burden of NuLBP.

Chapter 5 INVESTIGATION OF ONGOING PAIN IN CLBP USING ARTERIAL SPIN LABELLING

5.1 Introduction

In the previous chapter I described the morphological changes that were seen in CLBP and CLBP subgroups. In this chapter I will investigate the potential supraspinal functional neuroplastic changes that are associated with the ongoing experience of CLBP by observing regional cerebral blood flow (rCBF) as a correlate of neural activity.

This study has two main hypotheses:

1. There are differences in rCBF between CLBP and controls.

2. There are differences in rCBF between NuLBP and MLBP subgroups.

In this section I will discuss the challenges of measuring brain activity in CLBP. I will begin with a discussion of evoked experimental pain studies, then illustrate the limited amount of neuroimaging work that has attempted to describe the clinical experience of CLBP.

5.1.1 **Evoked Pain Studies**

There are substantial methodological difficulties in the analysis and measurement of brain activity associated with ongoing pain states, including LBP. Therefore, the majority of pain studies have measured brain activity using experimental evoked pain stimuli. Responses to acute pain stimuli given to healthy volunteers show a relatively consistent range of brain activation patterns (Tracey 2008), often referred to as the pain neuromatrix. Recently there has been a critical reappraisal of this concept questioning the significance of many acute pain studies and the consistency of their findings (Mouraux, Diukova et al. 2011). In contrast to acute pain, chronic pain studies show a wide variety of responses to experimental stimuli (Tracey 2008, Apkarian, Baliki et al. 2009, Davis and Moayedi 2013). Studies of clinical pain states including CLBP, show conflicting data – some show lower pain thresholds and increased neural activity to both local and distal stimulation; others show lower pain thresholds and increased neural activity to stimulation of the lower back only.

An MEG study of 10 low back pain patients with symptoms averaging 12 years in duration (no detail was given about the patients' symptoms other than none had neurological involvement), demonstrated lower pain thresholds to noxious electrical stimulation of the lumbar spine and increased power of the evoked field in low back pain patients compared to controls, relative to the chronicity of the subjects' symptoms (Flor, Braun et al. 1997). A more recent functional magnetic resonance imaging

(fMRI) study of mechanical pressure stimulation of the back in 6 subjects and 8 controls also showed lower pain thresholds with ratings of greater pain ‘unpleasantness’ in the CLBP group. Activation of an expansive network of pain-related brain regions, particularly in areas associated with the affective processing (prefrontal, insula, cingulate) and motor preparation (supplementary and premotor) was observed in both groups but at lower ratings of pain intensity in the CLBP group. At higher pain intensity, CLBP patients alone showed activation in the right thalamus (Kobayashi, Kurata et al. 2009). In contrast, Baliki et al showed no differences between CLBP and controls in pain thresholds to a noxious thermal stimulus to the back (Baliki, Geha et al. 2010).

Available studies also show conflicting data regarding decreased pain thresholds at sites away from the lower back. Flor et al. showed no differences in thresholds or MEG brain activity to stimulation of the index finger in CLBP patients compared to controls (Flor, Braun et al. 1997). Consistent with this, a group of 16 CLBP patients showed little difference in pain ratings and fMRI brain activity from control subjects to thermal stimuli to the back of the hand (Derbyshire, Jones et al. 2002). In contrast, both CLBP patients and fibromyalgia syndrome (FMS) patients showed decreased pressure pain thresholds at the thumbnail compared to controls (Giesecke, Gracely et al. 2004) although the somewhat more crude form of pain stimulus applied might explain this difference. All subjects, including controls, showed activation in similar areas to a painful

stimulus (contralateral primary and secondary [S2] somatosensory cortices, inferior parietal lobule, cerebellum, and ipsilateral S2).

The data above show conflicting evidence regarding distal pain thresholds and also conflicting evidence as to whether differences in pain processing and brain activity exist between CLBP subjects and controls. Data from previous sections of this thesis show that CLBP patients demonstrate increased tactile and 2PD thresholds, which have been associated with hypersensitivity to noxious stimuli in other studies, suggestive of altered central processing. Further work is needed to examine whether clinical, rather than experimentally evoked pain, shows differences in rCBF in CLBP patients compared to controls.

5.1.2 **Clinical Pain Studies: BOLD fMRI**

Clinical pain is fundamentally different, however, to stimulus-dependent experimental pain (Melzack and Wall 1996, Kupers and Kehlet 2006, Tracey and Mantyh 2007). Clinical pain is frequently tonic and ongoing. It may be spontaneously generated and have an unclear relationship with triggering factors. Pain perception may appear out of proportion to aggravating activities and may have uncertain spatial or temporal characteristics. Clinical pain may also demonstrate strong relationships with environmental, cognitive and affective components. Therefore, separate investigation of the neural characteristics of clinical pain is necessary. Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) is a suitable method to measure evoked,

stimulus-dependent experimental pain. However, BOLD presents with substantial methodological difficulties in the acquisition and analysis of the neural correlates of clinical pain and is problematic for measuring ongoing tonic pain or long-term treatment effects (Aguirre, Detre et al. 2002, Cahana, Carota et al. 2004). Its utility in chronic ongoing pain studies has therefore been questioned (Tracey and Johns 2010) (see section 5.1.4 for further discussion of this topic).

Apkarian and colleagues devised a method using a manual logging device to allow BOLD to be used to measure non-evoked pain (Apkarian, Krauss et al. 2001, Baliki, Chialvo et al. 2006). The subject in the scanner records the intensity of perceived pain via a finger-spanning device attached to the thumb and index finger. Placing the thumb and finger together corresponds to ‘no pain’ and stretching thumb and finger maximally apart corresponds to ‘maximum pain’. Brain regions involved in the finger-spanning task are excluded from the analysis or finger movement is treated as a confounder in a regression analysis. Using the finger-spanning device, brain activity in CLBP patients with spontaneous, non-evoked pain was measured while lying in the MRI scanner (Baliki, Chialvo et al. 2006). Although psychometric data were included in the supplementary material to the paper, there was no record of patients’ clinical diagnosis or mechanical or neuropathic presentation (However, when referring to the study in a later paper on spontaneous pain in (PHN) (Geha, Baliki et al. 2007) the authors state that the LBP patients were

considered neuropathic as they all had some degree of radiculopathy in their history).

The authors reported two essential phases of the spontaneous pain experience; a) when spontaneous pain was rapidly increasing and b) when spontaneous pain was at a sustained high level. During periods of increasing pain, activity was found in brain areas comparable to acute pain from noxious thermal stimulation to the finger, such as the insula, anterior cingulate cortex (ACC), multiple cortical parietal regions and the cerebellum. When the pain level was high and constant, however, a different pattern of activity was described; the medial prefrontal cortex (MPFC) was most active, with lesser activity seen in the amygdala and the ventral striatum. It was suggested ongoing pain was sustained by neural activity in the MPFC, in contrast to the multi-region activity associated with processing nociceptive information related to the initial pain experience. MPFC activity was strongly correlated with pain intensity and negatively correlated with DLPFC activity. The authors reflected this suggests a “tight interplay between brain activity, neuronal death, and cognitive abnormalities in chronic back pain” and that spontaneous CBP switches on the MPFC, the "emotional-mentalising region of the brain into a state of continued negative emotions (suffering) regarding the self, punctuated by occasional nociceptive inputs that perpetuate the state.”

I suggest that there may be problems with this interpretation. Firstly it suggests that there is a nociceptive basis for CLBP, in that the ongoing activity in the MPFC needs to be maintained by a nociceptive driver.

However, there is no real evidence of a relationship between CLBP and damage or pathology to the lumbar spine. Secondly, this interpretation seems to suggest a central brain locus for chronic pain in the MPFC (and in the relationship of the MPFC with the DLPFC), as if the experience of chronic pain can be concentrated in "a chronic pain centre". I would suggest that chronic pain is instead a multi-dimensional experience involving cognition, emotions and sensory dimensions, whose neural correlates involve multiple areas involved in processing these dimensions, rather than one sole centre. This is the central tenet of the work presented throughout this thesis and supported by the data from previous chapters.

Furthermore, I suggest that there are methodological problems with the use of the finger-spanning device in this study. Although, this study is predicated on demonstrating the neural correlates of spontaneous pain, the task demands inherent in the subject's use of the device means that brain activity is not related to a 'naturalistic' record of spontaneous pain alone. Although Baliki and colleagues state that activity relating to use of the device is excluded from the analysis or is treated as a confounder in a regression analysis, the use of subtraction designs has been criticised (Friston, Price et al. 1996). Brain activity involved in monitoring of sensory input and motor planning and execution is complex and involves the use of multiple systems and networks, which are not easily removed from the analysis. Most importantly, attentional or distractional and motor processes are known to modulate the experience of pain (Tracey,

Ploghaus et al. 2002, Valet, Sprenger et al. 2004). By using the device, attention is given to the pain, which may in itself be an important mechanism in the amplification of pain perception (Bantick, Wise et al. 2002); alternately, the device could in fact distract from the pain experience. In either case, I propose that Baliki and colleagues' study is therefore not a true record of pain in a resting state. In light of these criticisms I decided to explore alternatives to the use of BOLD fMRI to record non-evoked brain activity associated with chronic pain utilising Arterial Spin Labelling (ASL). An extensive critique of the limitations of BOLD together with a justification for the use of ASL (and potential alternative methodologies) are detailed in the following sections.

5.1.3 **Methods For Neuroimaging Of Chronic Pain**

5.1.3.1 **Positron Emission Tomography (PET)**

Positron Emission Tomography (PET) was used extensively in the 1990s before BOLD fMRI became the preferred medium for experimental pain studies. Several historical PET studies reported rCBF (regional cerebral blood flow) differences in the thalamus in cancer pain (Di Piero, Jones et al. 1991), neuropathic pain (Hsieh, Belfrage et al. 1995) and central pain (Peyron, Garcia-Larrea et al. 1995, Garcia-Larrea, Peyron et al. 1999) although one study showed thalamic hyperactivity in post-stroke pain (Cesaro, Mann et al. 1991). However, all of these studies used extremely small patient groups of between two and five subjects. Furthermore, these studies all used methods to reduce pain in their subjects, in order to compare the painful state with a pain-free state, rather than comparing

patients in pain with healthy controls. Evidence from structural and functional neuroimaging studies carried out since this early work and detailed throughout this thesis, shows that fundamental neuroplastic changes occur in patients with chronic pain, making them unsuitable for use as control subjects, even in the pain free state. In light of these limitations, care must be exercised in interpreting these studies. However, although PET is better suited than fMRI to examine brain blood flow and metabolic responses in ongoing pain, its use is limited, as it is invasive and expensive, requiring a radioactive tracer as a contrast agent to record a signal as it passes through tissue. It also demonstrates comparatively poor temporal and spatial resolution (Kupers and Kehlet 2006, Tracey and Mantyh 2007); inconsistencies in PET chronic pain data have been attributed to these technical limitations (Youssef, Gustin et al. 2014).

The last 15 years have seen BOLD fMRI become the dominant medium for imaging pain. Unfortunately, BOLD fMRI is not ideally suited to study clinical tonic pain states. These limitations of its usefulness in studying chronic pain are discussed below.

5.1.4 BOLD Presents With Methodological Difficulties In The Acquisition And Measurement Of The Neural Correlates Of Clinical Pain.

5.1.4.1 BOLD Is Not An Effective Technique For Recording Ongoing Neuronal Activity.

Although BOLD is a suitable method for recording phasic experimental pain stimuli, it is not ideally suited to record changes in neural activity over long periods of time (i.e. greater than 1 minute). This is due to susceptibility to noise contamination caused by low frequency drift in the scanner and physiological noise, which renders the use of BOLD problematic in inverse proportion to task frequency (Aguirre, Detre et al. 2002, Wang, Aguirre et al. 2003). BOLD, therefore, is not an effective technique for recording the ongoing neuronal activity at rest associated with tonic pain (Gusnard, Raichle et al. 2001, Owen, Clarke et al. 2010, Segerdahl, Xie et al. 2012).

5.1.4.2 BOLD Is Not Able To Record Absolute Baseline Measurements.

BOLD relies on a relative measure of contrast such as a before and after event-related task or experimental stimulus (Wang, Aguirre et al. 2003). Although BOLD is dependent on CBF (cerebral blood flow), BOLD signal changes cannot be expressed in quantifiable physiologic units but only as a percentage signal change or statistical significance level based on a statistical model. Measurements obtained are therefore relative, not quantitative. BOLD is not able to record absolute baseline

measurements, which limits the remit of conventional 'evoked-response' fMRI to assessing changes between states only. While BOLD imaging methodologies can be used to assess inter-relationships between brain regions (so-called 'resting-state' fMRI), this methodology is not included within the scope of this thesis.

5.1.5 **Arterial Spin Labelling (ASL)**

Recent advances in the use of arterial spin labelling (ASL) have enabled researchers to measure spontaneous pain in patients at rest over long periods, free from the signal to noise constraints inherent in BOLD fMRI technique (Howard, Krause et al. 2011). ASL relies on labelling the water content of inflowing arterial blood using radiofrequency pulses (Petersen, Zimine et al. 2006, Dai, Garcia et al. 2008). Unlike PET imaging, no radioactive tracers are required.

5.1.5.1 **ASL Is Able To Monitor Tonic Activity**

ASL is able to measure resting state basal activity as low frequency drifts are eliminated due to pairwise subtraction of tagged and control labeled images. It therefore offers improved sensitivity over BOLD in measuring neural activity for task frequencies of less than 0.006 Hz (ie periods of greater than 1-2 minutes) and therefore is ideal for measuring tonic pain states, characteristic of clinical pain (Aguirre, Detre et al. 2002).

5.1.5.2 **ASL Provides A Quantifiable Measurement Of rCBF**

ASL uses a quantifiable perfusion contrast rather than relative blood oxygenation contrast to measure functional brain activation (Wong 2014). The technique provides a non-invasive, in vivo quantitative measurement of blood flow, measured as the volume of blood that travels through tissue over time (ml/100g/min). Quantifiable units offer the desirable benefit of being able to compare directly differences across studies.

5.1.5.3 **ASL May Be A Better Marker Of Neuronal Activity Than BOLD**

It has also been suggested that ASL perfusion may be a better marker of neuronal activity as ASL measures just one physiological parameter (perfusion), whereas the BOLD signal is dependent on several physiological parameters including cerebral blood flow, cerebral blood volume and cerebral metabolic rate of oxygen uptake (CMRO2) (Menon 2001, Aguirre, Detre et al. 2002).

5.1.5.4 **ASL Demonstrates Superior Spatial Localisation Than BOLD**

In addition, ASL provides superior spatial localisation in areas of relevant neural activity, primarily recording signals from capillary beds. BOLD signal responses are more pronounced in venous draining networks in the region of activation, due to the low deoxhaemoyglobin level, resulting in a less uniform and more diffuse activation picture, compared to ASL (Aguirre, Detre et al. 2002, Duong, Yacoub et al. 2002, Wang, Aguirre et

al. 2003, Kim, Whyte et al. 2006, Petersen, Zimine et al. 2006, Huettel 2008, Liu, Hao et al. 2013).

In summary, ASL provides a quantifiable measurement of blood flow in the brain that allows for monitoring of low frequency activity (Petersen, Zimine et al. 2006). ASL has been shown to be effective in measuring experimental pain (Owen, Bureau et al. 2008, Owen, Clarke et al. 2010) Most importantly, the ability of ASL to study brain activity with prolonged stimuli and in particular, ongoing pain, makes it an ideal tool for measuring pain in chronic, clinical scenarios (Tracey and Johns 2010). ASL is increasingly being used to study diverse clinical conditions such as 3rd molar tooth extraction (Howard, Krause et al. 2011), migraine (Kato, Araki et al. 2010), osteoarthritis (Howard, Fotopoulou et al. 2012), low back pain (Wasan, Loggia et al. 2011) and neuropathic pain (Segerdahl, Xie et al. 2012, Liu, Hao et al. 2013, Youssef, Gustin et al. 2014).

5.1.5.5 **ASL In Studies Of CLBP**

Wasan and colleagues used ASL to examine the neural correlates of 16 patients with CLBP (Wasan, Loggia et al. 2011). The patients were a mix of those with predominantly axial pain and those whose main complaint was leg pain. The authors chose to study pain exacerbations provoked by clinical manoeuvres. In the axial group, pelvic tilting was chosen as the aggravating technique and in the patients considered to have radicular symptoms, a bilateral straight leg raising technique was employed. Each clinical manoeuvre was repeated 12 times and held for 10 seconds.

Patients were excluded from the study if their pain failed to return to baseline levels within 30 seconds after each stimulation. The authors stated that this allowed them to "distinguish between and assess pain exacerbations and ongoing chronic pain". They found significant activity in areas frequently associated with sensory-discriminative processing of experimental pain, such as S1, S2. They also found that medial prefrontal cortex and insula activity was associated with higher ratings of evoked pain.

Furthermore, Wasan and colleagues suggested that the use of clinical manoeuvres produced an experience analogous to chronic clinical pain rather than an experimentally induced pain experience. However, by choosing to examine neural activity associated with pain exacerbations, I would suggest that they, in fact, designed a study that investigates the neural correlates not of chronic pain but rather, of acute pain; arguably a phenomenon which has been previously studied using BOLD fMRI, albeit not directly using clinical manoeuvres. To choose to study manoeuvre-dependent acute pain rather than ongoing pain appears to be a missed opportunity to utilise the full ability of ASL to examine persistent spontaneous pain and to compare and contrast ASL data with the only previous study to attempt to study ongoing CLBP using BOLD (Baliki, Chialvo et al. 2006)(see section 5.1.2.2).

It should be noted that increased regional cerebral blood flow (rCBF) was only observed when pain levels had increased by greater than 30% in the CLBP group (it was not seen in thermal pain applied to the leg, which

caused a pain increase of approximately 19% in CLBP and only a transient pain increase in healthy controls). Therefore differences were only seen *within* CLBP subjects and between CLBP and controls at >30% pain increase. *No differences were reported between CLBP subjects and controls at rest (although this is not explicitly stated within the article).* One is therefore tempted to speculate that an exacerbation manoeuvre was consequently chosen in order to identify differences between groups.

The reasons why differences were not identified between CLBP and controls were not discussed by Wasan et al and remain unclear. Extensive developmental work from several members of our group has demonstrated clear differences between patients and healthy controls at rest, without additional stimuli, in 3rd molar tooth extraction (Howard, Krause et al. 2011) and osteoarthritis (Howard, Fotopoulou et al. 2012), employing a pseudo-continuous arterial spin labelling technique (pCASL). pCASL displays a superior signal to noise ratio of around 30% over pulsed arterial spin labelling (pASL), employed by Wasan et al.(Wong, Buxton et al. 1998, Luh, Wong et al. 1999, Dai, Garcia et al. 2008, Owen, Bureau et al. 2008). Furthermore, the specific pCASL implementation employed here utilises a fast spin echo (FSE) readout that does not suffer from susceptibility artifacts inherent in echo planar imaging (EPI) readout methodologies most commonly employed with pASL. By contrast FSE is much slower to collect a single volume, requiring approximately six minutes taken to collect a single volume for each pCASL sequence as compared to several seconds as may be expected using EPI.

I have therefore chosen this technique to examine not only differences in functional plasticity between controls and CLBP patients but also to explore differences between NuLBP and MLBP groups. This study is the first to my knowledge to use ASL to examine brain activity in spontaneous, non-stimulus dependent CLBP.

5.2 **Materials and Methods**

5.2.1 **Image Acquisition And Pre-Processing**

All ASL images were acquired during the same session as the structural scans taken for our VBM study, employing the same scanner and head coil. rCBF measurements were made using a pseudo-continuous arterial spin labelling technique (pCASL) (Dai, Garcia et al. 2008). We used exactly the same pCASL imaging sequence as used in recent studies in the same scanner (Hodkinson, Krause et al. 2013). Detail regarding this sequence is provided in the Appendix: 2. This sequence has been proven to be both reliable (Hodkinson, Krause et al. 2013) and sensitive to detect changes in regional cerebral blood flow that represent ongoing clinical pain in a resting state (Howard, Krause et al. 2011, Howard, Sanders et al. 2012).

5.2.2 **ASL Preprocessing**

Image pre-processing and analysis were carried out using Statistical Parametric Mapping software 8 (SPM 8) (Wellcome Department of Cognitive Neurology, London, UK, 2008; *www.fil.ion.ucl.ac.uk/spm*),

running under Matlab 7.12 (MathWorks, Natick, MA, USA). For each subject, the high-resolution T1-weighted structural images were used to align the data to MNI152 standard space (a T1-weighted brain image constructed from the average of 152 healthy individuals, collected at the Montreal Neurological Institute (MNI), Montreal, QC, Canada). Spatial normalisation was performed by co-registering each pCASL image to the segmented grey-matter (GM) image. Linear registration only was employed as the GM and pCASL images were from the same individual. The spatial normalization parameters required to warp the T1 image to MNI space were estimated (via SPM unified segmentation) and these parameters were applied to all the pCASL images. This strategy was adopted to reduce the likelihood of misregistration of the pCASL images. Finally, the images were spatially smoothed using a 10mm (full-width at half maximum) isotropic gaussian kernel to accommodate for gyral variability across subjects.

5.2.3 **Statistical Analysis Of ASL Data**

A voxelwise general linear model was used to identify differences between all three groups (controls, MLBP, and NuLBP) using one-way analysis of variance (ANOVA). For each subject, a simple average of the four rCBF maps was computed, which was used for groupwise analysis. Contrasts were specified comparing CBF values between MLBP, NuLBP and control groups. Global CBF values, in addition to age and gender, were included in the model as nuisance covariates.

Results were height thresholded at p<0.01, corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05 using the VBM8 toolbox in SPM8 developed by Christian Glaser *http://dbm.neuro.uni-jena.de/vbm/non-stationary-cluster-extent-correction/)*. Non-stationary cluster extent correction corrects for heterogeneity in the smoothness of the height thresholded corrected t-statistic and allows for valid cluster-level inference (Hayasaka and Nichols 2004). Use of non-stationary cluster extent correction has already been discussed in the MRI Statistical Analysis section of Chapter 2 (see 2.3.5.4).

For significant clusters, the mean rCBF values (in ml/100g/min) across all voxels within the cluster were extracted for each group individually and plotted as simple bar plots. Further statistical analysis of group differences on the extracted data was not employed in order to avoid the pitfall of circular analysis – so called “double dipping” (Kriegeskorte, Simmons et al. 2009). It is important to recognize that bar charts and tables are only representative, as they are raw summary estimates (means) of significant voxels identified in the mass univariate GLM analysis. Two important differences should be highlighted; (i) the mass univariate analysis identifies differences between groups having accounted for relationships between rCBF, global CBF, age and gender; (ii) significant clusters identified in the mass univariate analysis are inferred having accounted for non-stationarity across the image volume.

I also chose to explore the relationship of our between group data with psychological variables. I therefore chose to use the same approach that was taken with the VBM data of comparing the results of individual group regression analysis of the CES-D and STAI scores and rCBF and the ANCOVA group rCBF differences. Please see section 4.4 for a full account of the methods used.

5.3 **Results**

5.3.1 **CLBP Patients Demonstrate Reduced rCBF Compared To Controls.**

CLBP subjects demonstrated reduced rCBF compared to controls in a cluster extending posteriorly from the left lateral inferior division of the occipital cortex (visual cortex, V4, 5) extending anteriorly in to the middle temporal gyrus (temporo-occipital part) (see Table 57, Figure 52). Mean rCBF values are shown in Figure 53 and Table 58.

Table 57: Reduced rCBF in CLBP compared to controls

Cluster	Region	Cluster Size	Left				Right			
			T-Stat local maxima	x	y	z	T-Stat local maxima	x	y	z
1	Lateral occipital cortex (V5)	566	3.03	-48	-75	6	-	-	-	-
	Middle temporal gyrus		2.97	-52	-60	6	-	-	-	-

* rCBF = regional cerebral blood flow; Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak activation voxels in the cluster; x, y, z = orientations in MNI space.

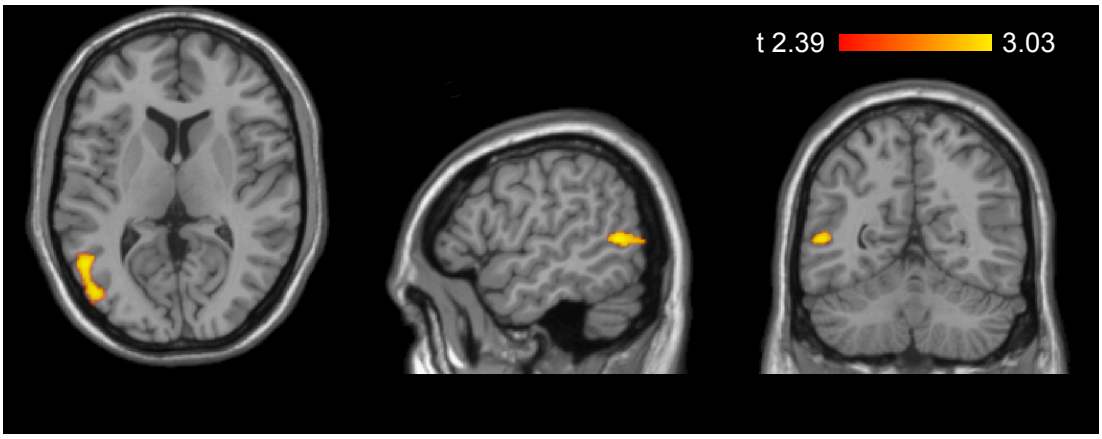

Figure 52: Reduced rCBF in CLBP compared to controls.

A cluster with reduced rCBF is seen in the lateral occipital cortex extending in to the left temporal gyrus.

* Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.03; Image is seen in neurological convention.

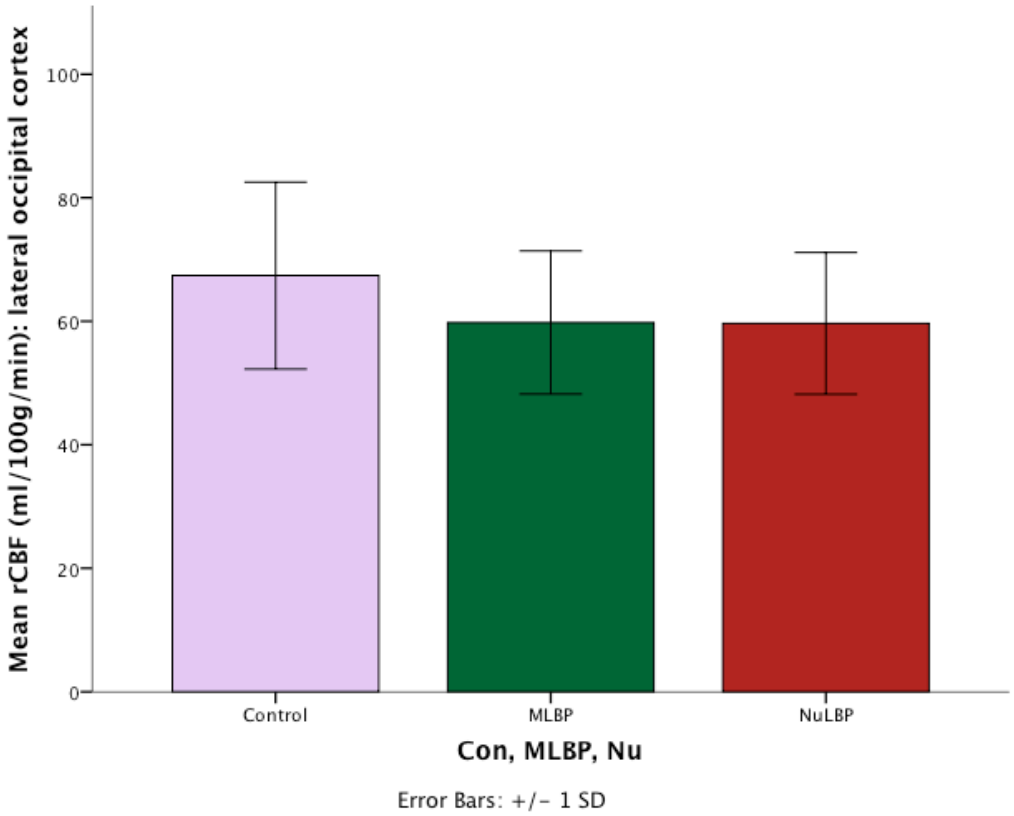

Figure 53: Mean rCBF values across groups (ml/100g/min).

Reduced rCBF in MLBP and NuLBP groups compared to controls is seen in the lateral occipital cortex

Table 58: Mean rCBF group values (ml/100g/min) for significant clusters.

SD = standard deviation, DLPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex, SCC = subcallosal cortex

Group	N	Lateral Occipital cortex		Insula		DLPFC		OFC		SCC		Superior parietal cortex	
		Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
Control	20	67.40	15.14	44.79	9.83	46.28	13.72	57.87	12.91	52.72	12.22	50.54	16.20
MLBP	24	59.79	11.57	44.28	9.10	45.28	12.28	56.16	12.26	49.64	10.35	46.10	9.82
NuLBP	22	59.66	11.48	43.99	7.55	40.28	8.43	52.39	8.89	45.21	8.71	49.40	10.25

5.3.2 **CLBP Patients Demonstrate Increased rCBF Compared To Controls.**

CLBP subjects showed increased rCBF compared to controls in a cluster extending anteriorly and superiorly in the right temporal pole into the anterior insula cortex, (see Table 59, Figure 54).

Table 59: Increased rCBF in CLBP compared to Controls.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat local maxima	x	y	z	T-Stat local maxima	x	y	z
1	Insula	267	-	-	-	-	2.92	36	14	-15
	Temporal pole		-	-	-	-	3.08	36	3	-23

* rCBF = regional cerebral blood flow; Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak activation voxels in the cluster; x, y, z = orientations in MNI space.

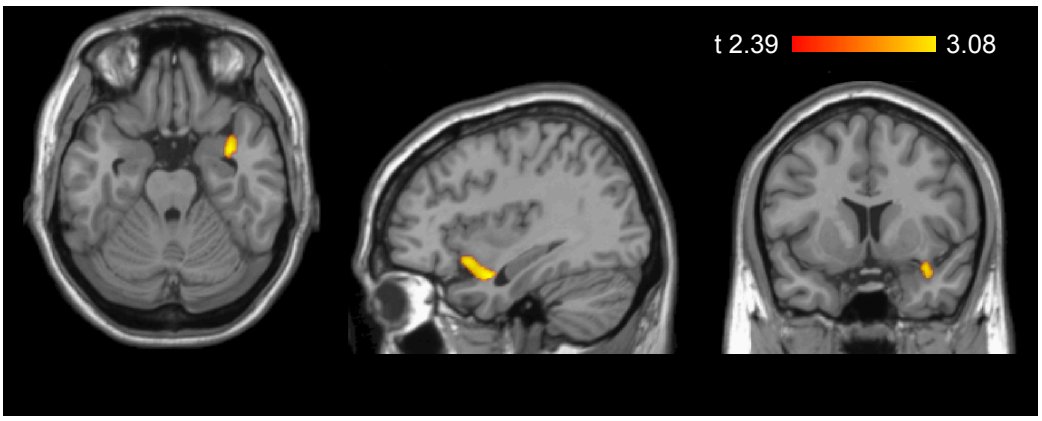

Figure 54: Increased rCBF in CLBP compared to Controls.

Increased rCBF is seen in a cluster in the right temporal pole and anterior insula.

* Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.08; Image is seen in neurological convention.

5.3.3 **NuLBP Patients Demonstrate Reduced rCBF Compared To MLBP.**

NuLBP subjects had reduced rCBF compared to MLBP subjects in a large cluster extending posteriorly from the left medial prefrontal cortex bilaterally into the subcallosal cortex and extending superiorly into the lower margins of the rostral anterior cingulate cortex. The left and right lateral borders of the cluster extended into the orbito-frontal cortex on either side. A further cluster was observed on the right in the frontal pole, anterior to the OFC (see Table 60,

Figure 55,

Figure 56).

Another large cluster was identified in the right orbitofrontal cortex (26, 24, -8), extending laterally and posteriorly and superiorly into the right anterior insula cortex (see Table 60,

Figure 55,

Figure 56).

One more cluster was seen in the dorsolateral prefrontal cortex extending anteriorly into the right superior frontal gyrus (see Table 59, Table 60,

Figure 55,

Figure 56).

Mean rCBF values are shown in Table 58 and Figure 57, Figure 58, Figure 59).

Table 60: Reduced rCBF in NuLBP compared to MLBP patients.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat local maxima	x	y	z	T-Stat local maxima	x	y	z
1	Nucleus Accumbens	2500	-	-	-	-	2.48	11	20	-9
	Subcallosal cortex		-	-	-	-	4.09	6	23	-26
	Medial prefrontal cortex		2.65	-3	45	-21	-	-	-	-
2	Dorsolateral prefrontal cortex	1706	-	-	-	-	3.26	36	15	60
3	Orbitofrontal cortex	1289	-	-	-	-	3.43	41	26	-5

* rCBF = regional cerebral blood flow; Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak activation voxels in the cluster; x, y, z = orientations in MNI space.

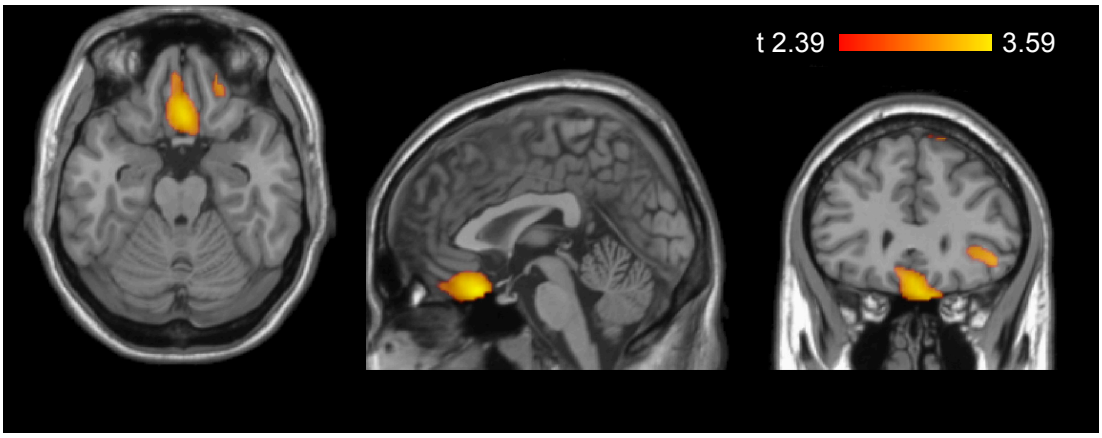

Figure 55: Reduced rCBF in NuLBP compared to MLBP patients.

Clusters were seen centrally encompassing the left medial prefrontal cortex, subcallosal cortex and lower margins of the rostral anterior cingulate cortex. Another cluster was seen in the right in the orbitofrontal cortex.

* Results are height thresholded at $p<0.01$ ($t=2.39$), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of $p<0.05$. Values of the t-statistic are colour coded, range is 2.39-3.58; Image is seen in neurological convention.

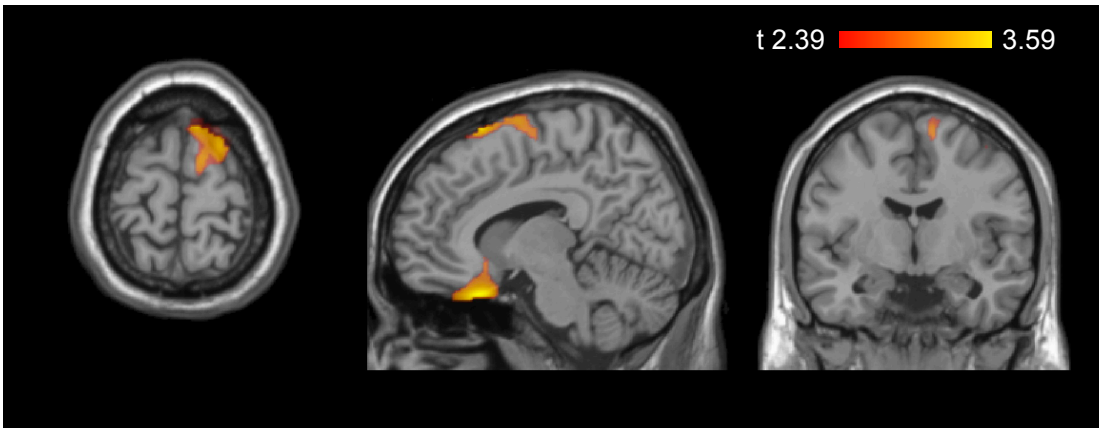

Figure 56: Reduced rCBF in NuLBP compared to MLBP patients.

Clusters were seen in the subcallosal cortex, superiorly in dorsolateral prefrontal cortex and in the right superior frontal gyrus.

* Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.03; Image is seen in neurological convention.

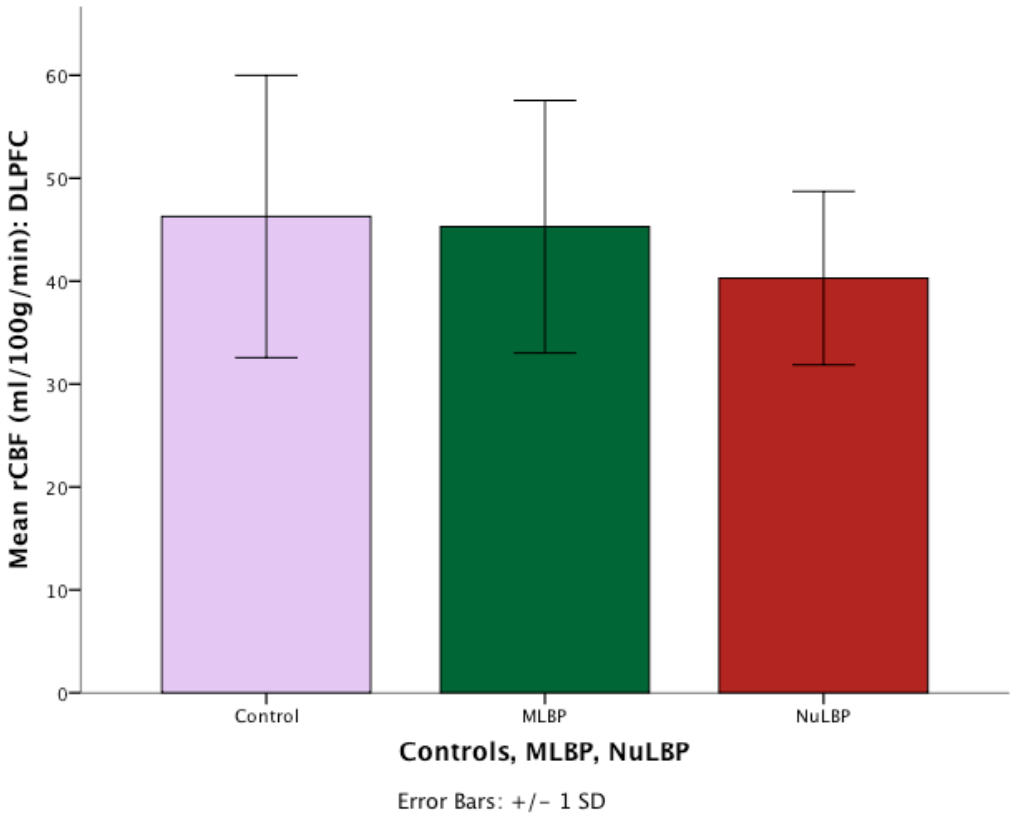

Figure 57: Mean rCBF values across groups (ml/100g/min)

Reduced rCBF in NuLBP patients compared to MLBP is seen in the DLPFC (Dorsolateral prefrontal cortex).

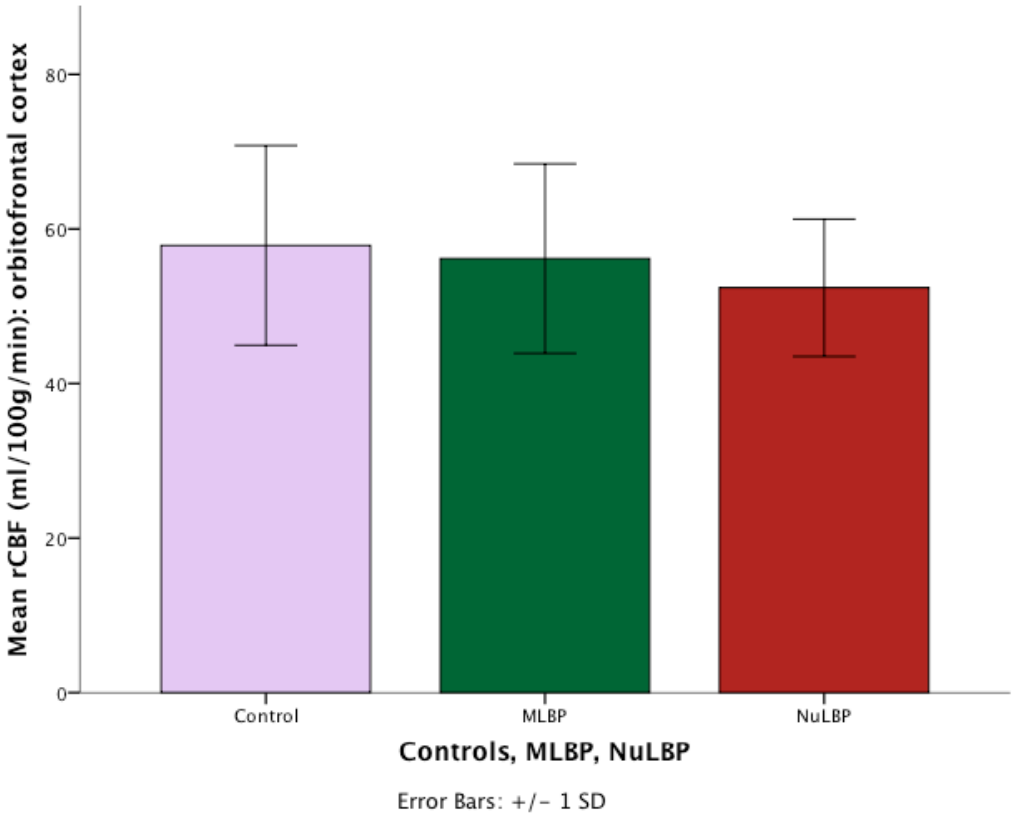

Figure 58: Mean rCBF values across groups (ml/100g/min)

Reduced rCBF in NuLBP patients compared to MLBP is seen in the OFC (orbitofrontal cortex).

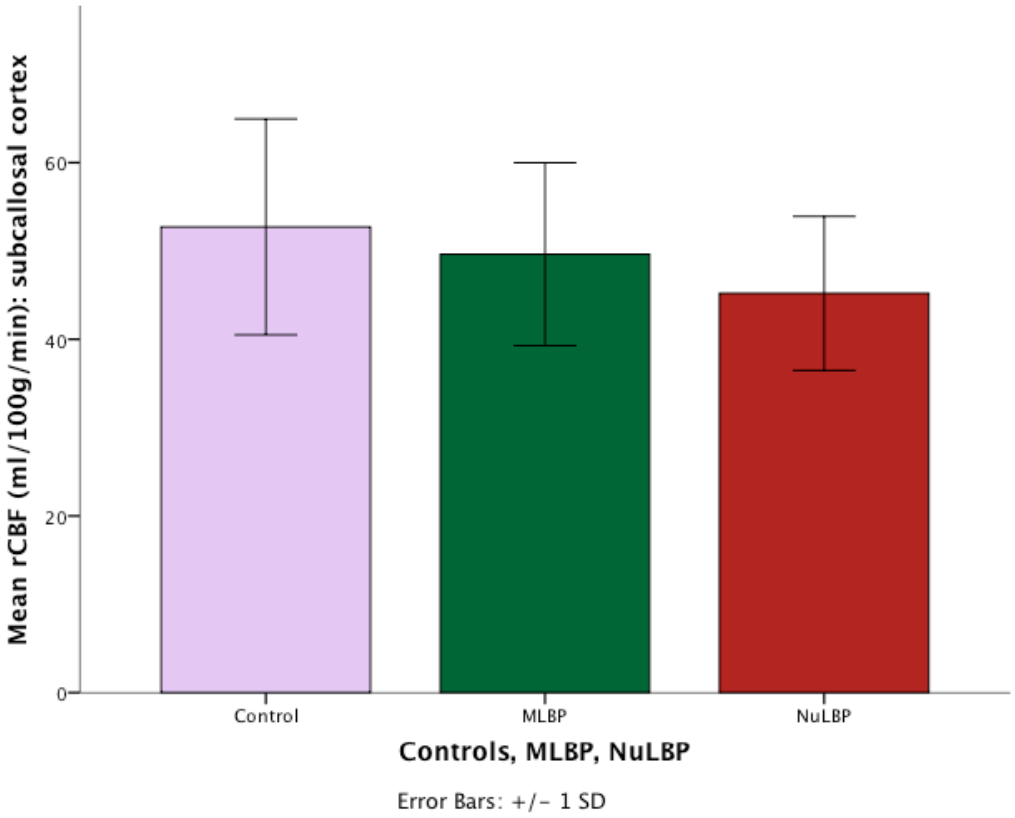

Figure 59: Mean rCBF values across groups (ml/100g/min).

Reduced rCBF in NuLBP patients compared to MLBP was seen in the SSC (subcallosal cortex).

5.3.4 NuLBP Patients Demonstrate Increased rCBF Compared To MLBP.

NuLBP subjects had increased rCBF compared to MLBP subjects in a cluster situated in the right posterior superior parietal lobule which extended immediately inferior and posterior into the superior division of the lateral occipital cortex (see Table 61, Figure 60).

Mean rCBF values are shown in Table 58 and Figure 61.

Table 61: Increased rCBF in NuLBP compared to MLBP.

Cluster	Region	Cluster Size	Left				Right			
			T-Stat local maxima	x	y	z	T-Stat local maxima	x	y	z
1	Lateral superior occipital Lobe	729	-	-	-	-	3.26	29	-83	23
	Superior parietal lobule	729	-	-	-	-	3.18	29	-72	41

* rCBF = regional cerebral blood flow; Region = brain region; Cluster size = number of voxels in the cluster; Left = left hemisphere, Right = right hemisphere; T-Stat local maxima = T value of peak activation voxels in the cluster; x, y, z = orientations in MNI space.

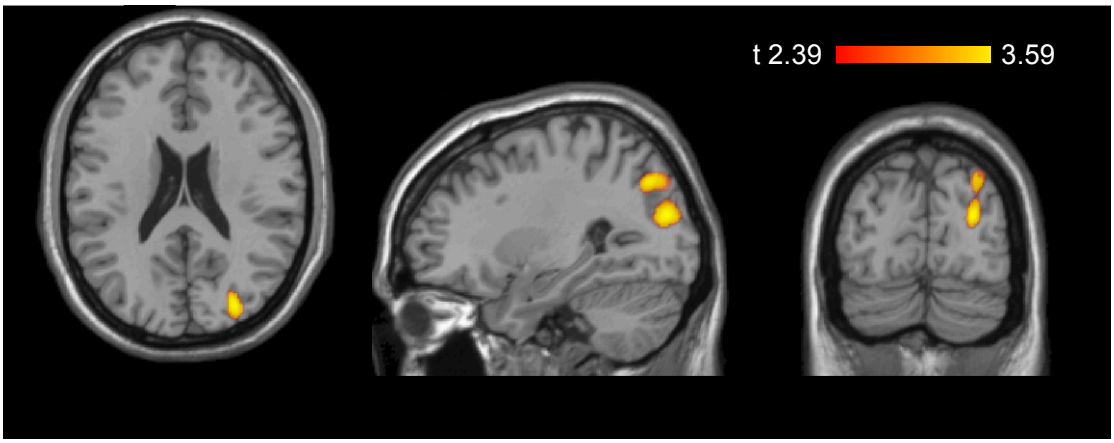

Figure 60: Increased rCBF in NuLBP compared to MLBP.

Clusters are seen in the right posterior superior parietal lobule and superior division of the lateral occipital cortex.

* Results are height thresholded at p<0.01 (t=2.39), corrected for voxelwise multiple comparisons using non-stationary cluster extent correction at threshold of p<0.05. Values of the t-statistic are colour coded, range is 2.39-3.59; Image is seen in neurological convention.

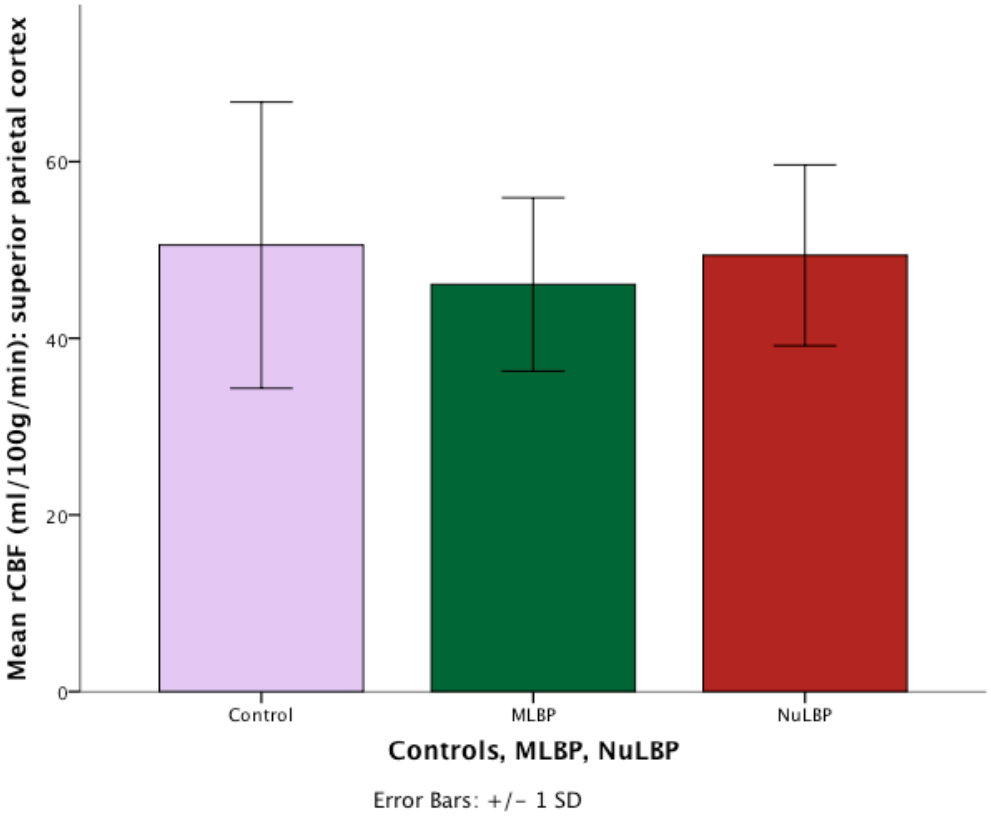

Figure 61: Mean rCBF values across groups (ml/100g/min).

Increased rCBF in NuLBP patients compared to MLBP was seen in the superior parietal cortex.

5.3.5 **Regression analysis**

5.3.5.1 **CES-D**

Comparison of regression analysis using CES-D with analysis of group differences (ANOVA) showed negligible overlap in areas in which rCBF alterations were observed.

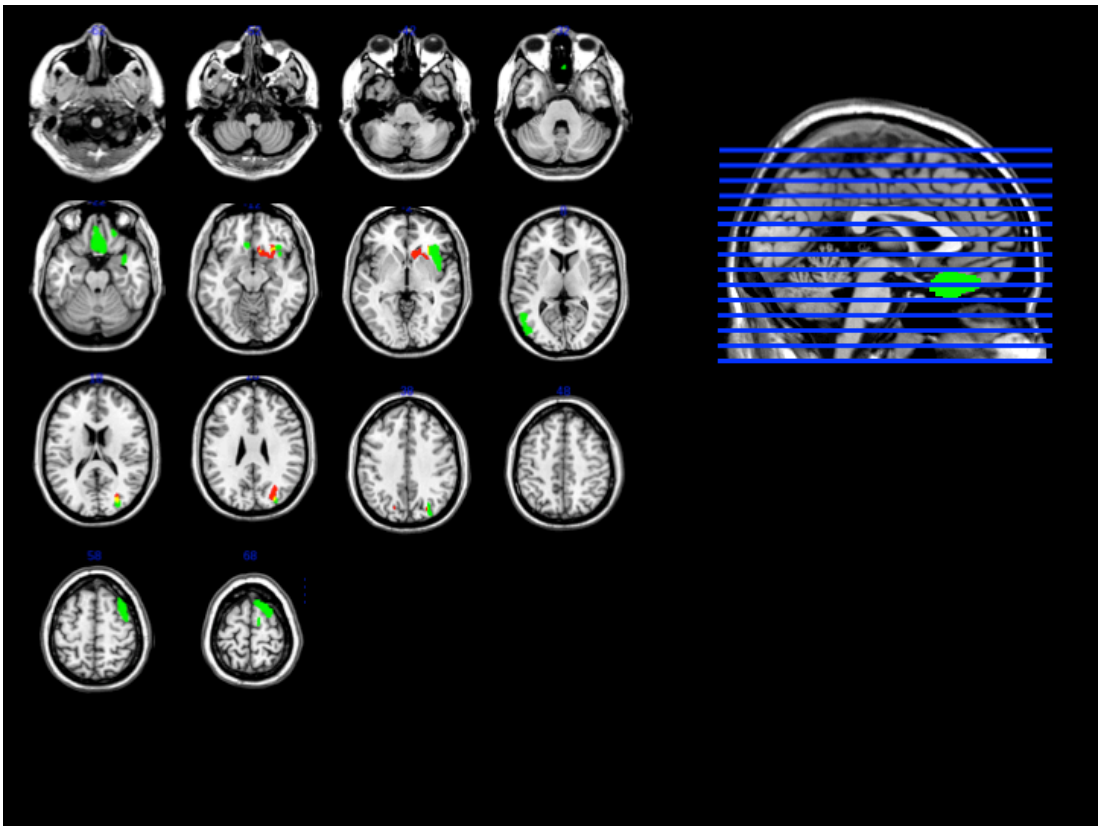

Figure 62: Composite image showing results of a) analysis of group differences (ANOVA) and b) CES-D regression analysis.

Areas in green show all significant alterations in rCBF (increases or decreases) between groups (ANOVA: CLBP & controls, MLBP & NuLBP). Areas in red show significant relationships between alterations in rCBF (increases or decreases) and CES-D scores (Regression analysis). Areas in yellow show areas of alterations in rCBF common to both analyses.

5.3.5.2 **STAI-state**

Comparison of regression analysis using STAI-state with analysis of group differences (ANOVA) showed negligible overlap in areas in which rCBF alterations were observed.

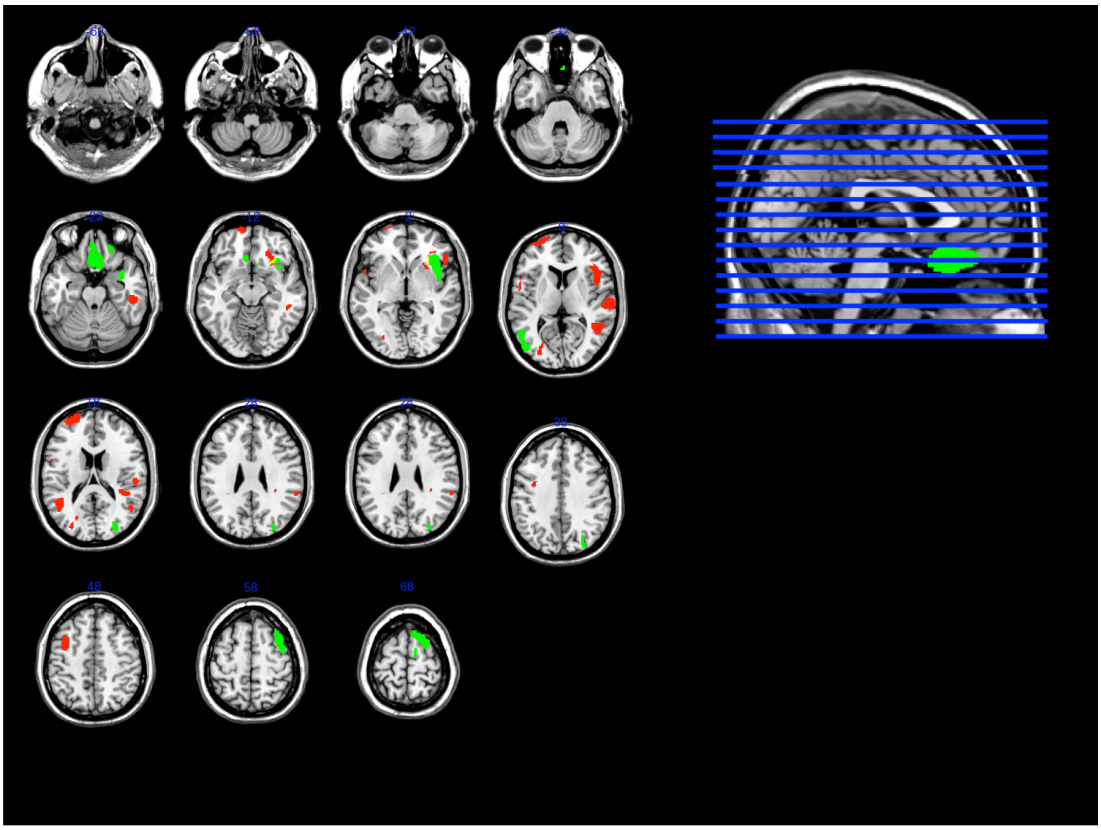

Figure 63: Composite image showing results of a) analysis of group differences (ANOVA) and b) STAI-state regression analysis.

Areas in green show all significant alterations in rCBF (increases or decreases) between groups (ANOVA: CLBP & controls, MLBP & NuLBP). Areas in red show significant relationships between alterations in rCBF (increases or decreases) and STAI-state scores (Regression analysis). Areas in yellow show areas of alterations in rCBF common to both analyses.

5.4 Discussion

5.4.1 Summary Of Results

We have demonstrated significant differences in rCBF not only between patients with CLBP and controls but also between MLBP and NuLBP patients.

Patients with CLBP showed reduced rCBF in the middle temporal gyrus and increased rCBF in the right anterior insula cortex compared to controls. NuLBP subjects demonstrated reduced rCBF compared to MLBP subjects in the medial prefrontal cortex, subcallosal cortex, anterior cingulate cortex, orbito-frontal and insula cortex and dorsolateral prefrontal cortex.

In the following sections I will describe rCBF increases and decreases initially in comparison of CLBP with controls, followed by alterations in rCBF in NuLBP compared to MLBP sub-groups.

5.4.2 Patients With CLBP Show Reduced rCBF In The Middle Temporal Gyrus Compared To Controls.

Patients with CLBP showed reduced rCBF compared to controls in a cluster extending posteriorly from the left lateral inferior division of the occipital cortex (visual cortex, V4, 5), extending anteriorly in to the middle temporal gyrus (temporo-occipital part). This area has been described as the extrastriatal body area (EBA) and proposed as a key area involved in processing the visual appearance of the body, as opposed to facial

recognition (Downing, Jiang et al. 2001). It may be involved in appreciation of the configuration of movement and action (Downing, Jiang et al. 2001). Importantly, it may be involved in regulation of the body schema (the sense of the body, its position, posture and appearance in space) via proprioceptive input and/or communication via motor networks (even in the absence of visual feedback) (Astafiev, Stanley et al. 2004), thereby dynamically updating bodily representation via sensory and proprioceptive feedback during movement. Activation of the EBA has also been implicated during observation of 'emotional' body postures (Peelen, Atkinson et al. 2007). Although it is assumed that altered posture, movement patterns, and motor function seen in CLBP are a consequence of local pathology (Jull and Richardson 2000), I suggest they may also have a relationship with the affective component of CLBP as seen in this study's behavioural and VBM data. For instance, fear of movement is associated with muscle guarding and 'bracing'. The maintenance of aberrant movement patterns, often associated with muscle 'dysfunction' by physiotherapists, may also be linked to an emotional reaction to back pain (Hodges and Moseley 2003). The behavioural and VBM data from this study has shown that there is a large affective component to the experience of CLBP, which may be linked to these 'emotional' body postures. Although the EBA is a visual processing area, the involvement of the EBA in monitoring bodily movement does not necessarily depend on visual feedback (Astafiev, Stanley et al. 2004). The EBA may have an important role in monitoring movement in an environment or context specific manner, where movement and task completion has changed from being effortless and thoughtless, in a healthy individual, to

uncertain and challenging, consistent with reports from patients with CLBP (Lethem, Slade et al. 1983, Linton 2000, Vlaeyen and Linton 2000, Leeuw, Goossens et al. 2007).

I suggest that reduced perfusion in the EBA may represent the demands of monitoring posture, movement and maintaining a coherent body schema in response to profound changes in motor function, proprioceptive input and aberrant afferent input. This is consistent with the notion of embodiment and enmeshment (Osborn and Smith 2006) discussed previously and suggest that together these data add further evidence to the proposal that alterations in body schema and sense of self-identity are present in CLBP due to alterations in motor, and representational networks.

Future work is necessary to explore the directional relationships between alterations in posture and movement patterns (negative 'emotional 'postures) and negative emotional states and cognitive impairment. Damasio's somatic marker hypothesis (Damasio, Grabowski et al. 2000, Damasio 2005), states that bodily signals (i.e. initial pain and spasm as a consequence of local pathology) give rise to emotional states that influence decision-making (i.e. 'gut feelings'). These data also need to be examined in relation to existing evidence of the cognitive impairment seen in patients with CLBP. Impaired neuropsychological performance (NP) has been demonstrated previously in patients with osteoarthritic CLBP compared with pain-free subjects. In particular, CLBP patients were found to have deficits in attention, visual-spatial awareness, mental flexibility and mental dexterity. Pain severity was inversely correlated with NP performance (Weiner, Sakamoto et al. 2006).

Specifically, CLBP patients were impaired on the IOWA gambling task, a task designed to assess 'real-life' decision-making. Task performance was negatively *related to pain intensity at the time of the task.* The deficits in emotional decision-making did not occur in healthy patients subject to an acute pain stimulus. The authors suggested that chronic pain engages areas of the brain involved in emotional cognitive processing which may not be activated in acute pain conditions. Engagement of these emotional processing areas may have clinical correlations in the levels of distress that chronic pain patients feel and performance in emotional decision-making (Apkarian, Sosa et al. 2004). In particular, the frontal regions in which we observed reductions in rCBF in in NuLBP patients (DLPFC and orbito-frontal cortex) have been associated with reduced levels of N-acetyl aspartate (NAA) shown in magnetic resonance spectroscopy (MRS) studies of CLBP (Grachev, Fredrickson et al. 2002, Grachev, Ramachandran et al. 2003) Reductions in NAA levels are typically a sign of neuronal loss or damage in pathologic conditions involving neurons such as multiple sclerosis, Alzheimer's disease and stroke (Befroy and Shulman 2011). Other pain studies using MRS have also shown reductions in NAA and other metabolites and neurotransmitters such as glutamate and glutamine in migraine (Prescot, Becerra et al. 2009), neuropathic pain (Fukui, Matsuno et al. 2006) and spinal cord injury (SCI) (Pattany, Yezierski et al. 2002). Siddall and colleagues have stated that MR spectroscopy data in conjunction with a pattern recognition method (Statistical Classification Strategy) can differentiate between subjects with CLBP and healthy controls with a reported accuracy of between 97-100% (Siddall, Stanwell et al. 2006). This

data relates directly to the potential for chemical neuroplasticity in CLBP. Given the multi-system changes observed in persistent pain demonstrated by the convergent behavioural, functional and structural neuroplastic changes observed in this thesis, chemical neuroplastic sequelae are inevitable.

The relationship between cognition, emotional distress and, in particular, underlying neuropathic or mechanical pain mechanisms needs further investigation. In addition to cognitive dysfunction, changes in neurotransmitter and metabolite concentration in frontal brain areas and elsewhere have led to the suggestion that neuro-degenerative processes should also be considered as an additional contributor to the psychological and behavioral maladaptive coping strategies that CLBP patients demonstrate. As neuropathic pain patients are reported to complain both of greater physical and psychological distress (Dworkin 2002) these findings may reflect a common neurobiological substrate for psychological co-morbidities and chronic neuropathic pain. Furthermore, the same changes in cognitive function may contribute to the refractory nature of CLBP and reduce the likelihood of successful intervention. Whether the processes underlying intractable clinical pain are neurodegenerative, i.e. truly irreversible, remains a contentious topic; it is undoubtedly complex and may well be underpinned by multiple processes, for example, specificity of initiating underlying disease state, psychometric profile, pain intensity and chronicity of symptoms (Pleger, Dinse et al. 2001, Pleger, Tegenthoff et al. 2005, Pleger, Ragert et al. 2006, May 2008, Gwilym, Filippini et al. 2010).

5.4.3 Patients With CLBP Show Increased rCBF In The Anterior Insula.

In addition, we observed increased rCBF in the anterior insula in CLBP patients, compared to individuals in the control group. The anterior insula is a key area involved in monitoring information about the condition and location of the body, stimulus saliency (including pain) and the internal and external environment. This region has been discussed at some length in the previous chapter. It is suggested that the insula is a hub that monitors the external and internal world in order to produce overall awareness of the present moment, described by Craig as a “global emotional moment” (Craig 2009). I propose that involvement of this region is further evidence of the negative impact of CLBP not just on a sensory level but on a profound level that affects the well-being of the sufferer in all respects.

To summarise, the two areas we have identified as showing significant alterations in rCBF in CLBP patients compared to controls are both involved in monitoring and regulating the internal and external environment and are crucially involved in monitoring motor performance. I also suggest that they may have an important role to play in the maintenance and regulation of body schema and are adversely affected in CLBP.

5.4.4 **Comparison Of NuLBP With MLBP Patients Shows rCBF Reductions In The Subcallosal Cortex.**

NuLBP subjects had reduced rCBF compared to MLBP subjects in a large cluster that included the left medial prefrontal cortex, bilateral subcallosal cortex (SCC) and the rostral anterior cingulate cortex. Additionally reductions were seen in a cluster in the right OFC and anterior insula and in the right DLPFC and SFG. Increases were seen in a cluster in the superior parietal and lateral occipital cortex.

I suggest that the reductions in rCBF observed in the SCC, OFC, DLPFC reflect alterations in networks involved in multiple functions concerned with evaluation and maintenance of homeostasis. Alterations in grey matter volume and rCBF reported in the SCC, subgenual ACC (sACC), DLPFC and orbitofrontal cortex and are associated with various mood disorders (Sheline 2003, Drevets, Price et al. 2008), particularly depression (Mayberg, Lozano et al. 2005, Hajek, Kozeny et al. 2008). Failure of homeostatic self–regulation in these brain areas under conditions of “cognitive, emotional, or somatic stress” has been suggested as a mechanism underpinning long term depression (Mayberg 2009). The behavioural data of this cohort was reported in chapter 2. The psychometric correlates of cognitive, emotional, or somatic stress in CLBP patients (compared to controls) and, in particular, NuLBP patients (compared to MLBP) were discussed. These findings are consistent with studies that report significantly lower quality of life scores across a number of domains in individuals with neuropathic pain (Dworkin 2002, Jensen, Chodroff et al. 2007). Furthermore, there is increasing

evidence that neuroimmune mechanisms may underlie depression and pain comorbidity (Walker, Kavelaars et al. 2014). In fact, Mayberg's theory of dysregulation of prefrontal and cortico-limbic homeostatic mechanisms in depression may also apply to the unhappy triad of neuropathic symptoms, pain intensity and low mood.

I suggest that the data from this study provide evidence in support of a theory that the SCC mediates the behavioural experience of both high pain intensity and low mood associated with NuLBP. Preclinical anatomical studies show SCC projections to and from multiple areas that may support a dual mechanisms theory of pain and depression. These areas include the periaqueductal grey matter, nucleus accumbens, brainstem, insula, hypothalamus and hippocampus (For a review of SCC connections see (Mayberg 2009) and (Hamani, Mayberg et al. 2011)). However, although form and function may be linked, they are not the same. The additional use of other modalities is necessary in order to explore the relationships between brain regions and the multi-dimensional experience of pain. Increasingly, fMRI has been used to examine functional connectivity between brain regions in so-called resting state networks (RSN) (Biswal, Yetkin et al. 1995, Xiong, Parsons et al. 1999, Hampson, Peterson et al. 2002). Several studies have explored connectivity in specific networks associated with evoked experimental pain, mostly using healthy volunteers (Davis and Moayedi 2013). Recently a study explored sustained evoked pain using a pressure cuff, arguing that its longer duration had a greater relevance to clinical pain and found that the somatotopic representation of the stimulated leg in the

somatosensory cortex became less connected to the sensorimotor RSN and more to regions associated with the salience RSN (Kim, Loggia et al. 2013).

Functional connectivity has been reported in spontaneous, non-evoked clinical pain between the DMN and the insula cortex in fibromyalgia syndrome (Napadow, LaCount et al. 2010, Napadow, Kim et al. 2012). Loggia and colleagues (Loggia, Kim et al. 2013), using the same CLBP patient group and pain exacerbation protocol as in a previous study (Wasan, Loggia et al. 2011) examined functional connectivity in the default mode network (DMN), a network of regions that are active when the brain is not involved in a specific task, i.e. at rest (Raichle, MacLeod et al. 2001). Loggia et al were able to observe differences between patients and controls at baseline using functional connectivity (patients showed stronger DMN connectivity with the pregenual anterior cingulate cortex (pACC), insula and inferior parietal lobule. After pain exacerbation, greater pain was associated with *reduced* connectivity between the DMN and the pregenual anterior cingulate cortex and *greater* connectivity between the DMN and insula. While the mechanisms underpinning the correlations between brain regions, as revealed by resting-state fMRI, remain poorly understood (Castellanos, Di Martino et al. 2013), the technique offers promise in the understanding of clinical ongoing pain. I hope to explore the potential relationships between brain activity as seen in this study and functional connectivity across brain networks in future work.

5.4.5 **Patients With NuLBP Show Reduced rCBF In The Anterior Insula.**

Interestingly, reductions were seen in the anterior insula, in contrast to the *increases* in a more inferiorly situated cluster, seen in CLBP compared to controls. Activation in the anterior insula has been observed in response to brush-evoked mechanical allodynia in neuropathic pain patients (Schweinhardt, Glynn et al. 2006). The anterior insula is involved in monitoring internal and external environments in order to arrive at an evaluation of the present moment (see 5.4.3). I suggest that increases in anterior insula rCBF in CLBP patients reflect a system actively working (or possibly overworking) to monitor and evaluate the internal and external perturbations of CLBP across a broad range of domains. However, I suggest that rCBF *reductions* in the anterior insula in NuLBP patients reflect evaluative and mentoring processes that are struggling to cope or possibly shutting down, in response a clinical picture of chronic NuLBP that is increasingly demanding and possibly overwhelming. Further work is needed to examine the relationship between brain activity and the ability to cope with ongoing pain and distress (using measurements such as the Chronic Pain Coping Inventory (Jensen, Turner et al. 1995) or the Coping Strategies Questionnaire (Rosenstiel and Keefe 1983) in neuropathic and non-neuropathic LBP patients.

5.4.6 NuLBP Patients Show rCBF Increases In The Right Posterior Superior Parietal Cortex

rCBF increases were also observed in the right posterior superior parietal cortex. Posterior areas of the parietal cortex have been described as 'integrative' or 'associative' areas involved in multisensory integration of information relating to the representation of the state of one's own body (Wolpert, Goodbody et al. 1998, Azanon and Haggard 2009, Longo, Azanon et al. 2010). Lesions to this area are associated with disruption to this internal representation (Daprati, Sirigu et al. 2010). Interestingly, it appears to share similar functions with the EBA, namely regulation of the body schema via integration of sensory and motor information (Azanon and Haggard 2009). Whereas the somatosensory cortex, located in the anterior aspect of the parietal lobe is associated with primary somatosensory functions of localisation and discrimination of sensory input, the posterior parietal regions are associated with so-called 'higher' somatosensory functions of multisensory integration of sensory information, representation of the body schema (Tsakiris, Costantini et al. 2008) and dynamic representation of the body moving through space (Bolognini and Maravita 2007). I suggest that increases in rCBF in this area together with the rCBF changes seen in the EBA, demonstrate the involvement of networks dedicated to the maintenance and regulation of the state of the body under threat from an increasing sensory, cognitive and affective load. Further work is required to explore relationships between areas involved in representation of the body schema and body image (De Preester 2005), examination data (proprioception, sensory discrimination) and qualitative analysis of sense of

ownership of the body and self-identity (De Preester 2005, Osborn and Smith 2006).

5.5 **Conclusion**

The aims of this chapter were to investigate two main hypotheses:

1. There are differences in regional cerebral blood flow (rCBF) between CLBP and controls.

2. There are differences in regional cerebral blood flow (rCBF) between NuLBP and MLBP subgroups.

These results show significant differences in rCBF between CLBP and controls and between NuLBP and MLBP subgroups. Most importantly, we have been able to identify alterations in brain activity that clearly distinguish CLBP phenotypes. I have argued that the changes in rCBF in NuLBP patients, in particular, reflect a maladaptive functional plasticity as a result of the increasing sensory, cognitive and affective burden of NuLBP, further supported by the behavioural, examination and structural data already reported in this thesis.

In comparison to the widespread alterations in GM seen in the VBM data, there are relatively fewer areas of rCBF alterations identified in the ASL data. As the two methodologies are entirely different there is no reason that the results should be equivalent. As detailed in section 5.1.5.5, methodical aspects of ASL data acquisition (in particular, the relatively poor signal to

noise ration of ASL) make collection of the ASL signal challenging. However, in contrast to a previous CLBP study using ASL, this study is the first to identify differences in rCBF in back pain patients at rest.

In addition, as detailed in sections 5.1.5 & 5.1.5.4, ASL provides superior spatial localisation compared with BOLD in areas of relevant neural activity, with less contamination of signal from venous draining networks. This results in a more localized and less diffuse activation picture, compared to BOLD.

It is difficult to compare the results of this ASL study with other studies due to the use of different methodologies (PET, BOLD fMRI), different paradigms (evoked and non-evoked pain) and a wide variation in study sizes. However, the only other CLBP study to examine non-evoked pain in the scanner also demonstrated a discrete activation pattern in contrast to the widespread patterns seen in evoked pain studies (Baliki, Chialvo et al. 2006). Further studies are required to examine clinical rCBF profiles of different clinical conditions using this methodology. Only very recently have studies by Liu et al (Post-Herpetic Neuralgia -PHN) (Liu, Hao et al. 2013) and Youseff et al (Trigeminal Neuropathy - PTN, Temperomandibular Disorder- TMD) (Youssef, Gustin et al. 2014) related to ongoing clinical conditions rather than pain evoked by tissue damage or mechanical pressure (OA, tonic muscular pain). Together this latter study and the results presented here provide evidence to suggest that different clinical conditions are likely to demonstrate different functional profiles, just as have been shown in morphometric structural MRI studies (Tracey and Bushnell 2009, Lee and Tracey 2010, Apkarian, Hashmi et al. 2011, Lee and Tracey 2013).

In particular, more studies need to be undertaken to compare and contrast neuropathic and non-neuropathic clinical phenotypes using this methodology. The rCBF profiles of neuropathic and mechanical CLBP subgroups demonstrated by this study are markedly different from the profiles of PTN and TMD groups shown in the recent study by Youssef et al (Youssef, Gustin et al. 2014). Evidence suggests that different functional imaging profiles may exist within neuropathic pain itself, relating to different mechanisms underlying the different clinical presentations of neuropathic pain. For instance, fMRI studies of allodynia show no unique allodynic cortical signature or network - mechanical and cold allodynia show differences in brain activation patterns, with cold allodynia showing similar cortical activation patterns to normal cold pain in patients with syringomyelia (Ducreux, Attal et al. 2006). I suggest that neuropathic pain is not an homogenous 'all-or-nothing' state but rather an heterogeneous condition whose multiple clinical profiles reflect a wide variation in underlying neuropathic pain mechanisms. Vital further work needs to be undertaken to match clinical symptom clusters and sensory testing profiles of neuropathic pain patients with functional and structural imaging data to better understand similarities and differences in neuropathic pain in CLBP and beyond.

Chapter 6 GENERAL DISCUSSION

6.1 Overview

The aim of this study was to demonstrate differences in behavioural, examination and functional and structural neuroimaging data between CLBP patients and controls and, in particular, between NuLBP and MLBP patients.

In chapter 3, significant differences were identified between CLBP patients and controls and between NuLBP and MLBP patients in multiple behavioural domains measuring sensory discriminative dimensions of pain, function and psychological well-being and distress. Significant differences were also identified between CLBP patients and controls and between NuLBP and MLBP in tactile threshold discrimination and between CLBP patients and controls in two-point discrimination. In chapters 4 & 5, using functional and structural neuroimaging, we identified significant differences in CLBP patients and controls and between NuLBP and MLBP patients in widespread regions to do with evaluation and assessment, decision-making and planning, mood and emotion, modulation of pain and representation of the body schema.

The following discussion highlights the main themes and issues that have been identified in this thesis. Future directions for further research are also suggested.

6.2 **Brain resources are devoted to the evaluation of threat and stimulus saliency.**

The data from this study show the impact of CLBP on the individual, in terms of physical and psychological suffering, particularly in the CLBP patients that were identified by painDETECT as having a significant neuropathic component. Chronic pain is a stressor, as it is a threat to well-being and homeostatic balance (Sapolsky 2004). The behavioural data show not only evidence of increased levels of pain, functional disability and physical health problems but also greater levels of anxiety, depression and general mental health problems in CLBP patients and, in particular, NuLBP patients. The observed association of on-going pain intensity with reduced psychological well being may overwhelm the ability of the individual to maintain normal physiological functioning (allostasis) and lead to allostatic systems becoming dysregulated. Changes to physiological maintenance systems, including neuroimmune functioning, may lead to an amplification and prolongation of the pain state by mechanisms that include changes to brain structure and function (Borsook, Maleki et al. 2012, Vachon-Presseau, Roy et al. 2013). The imaging data reported here revealed several regions that may be involved in mediating and regulating mood and affective components of the pain experience. A novel finding was reduced rCBF in the SCC in NuLBP patients, an area that has been associated with long-term depression. We also observed GM alterations in the DLPFC, orbitofrontal cortex, hippocampus, basal ganglia and ACC. These areas have well established roles in the processing of the affective components of the pain experience

and are also implicated in low mood and depression. We also observed GM reductions in the hippocampus in NuLBP patients compared to controls. Reduced hippocampal volume is also associated with major depression (Lee, Reif et al. 2013) and has been observed in patients with CLBP, in conjunction with increased levels of cortisol and activation in the anterior parahippocampal gyrus, suggestive of a sustained stress response (Vachon-Presseau, Roy et al. 2013). I propose that together, the changes within the hippocampus, SCC, DLPFC, orbitofrontal cortex, basal ganglia and ACC are likely to be associated with mediating the stress and low mood that patients with CLBP demonstrate in our behavioural data, and to a significantly greater extent, in the NuLBP population.

A key finding of the neuroimaging chapters of this study is the amount GM alterations in brain regions devoted to evaluation and assessment of stimulus saliency such as the cingulate cortex and anterior insula. Our data show that patients with CLBP are involved in an on-going assessment of internal and external stimuli, in order to evaluate potential threats and rewards based on the saliency of competing stimuli in areas such as the OFC, anterior insula, basal ganglia and DLPFC. I suggest that as pain increases, it becomes increasingly more threatening to the sufferer and therefore increasingly salient, resulting in higher states of alertness and responsiveness to both painful and non-painful stimuli seen in patients with CLBP. I suggest that GM alterations observed in the salience network and planning and evaluative regions reflect the hypervigilance shown by patients as internal and external inputs become increasing more of a threat (Asmundson and

Hadjistavropoulos 2007). GM loss and alterations blood flow in the imaging data suggest that patients with CLBP devote increasing resources to planning, evaluation and decision making. It is unclear whether these alterations are adaptive and reflect a system coping with increased demand or maladaptive, reflecting evaluative and decision-making networks that are no longer able to cope.

As pain increases, decision-making becomes increasing problematic as the rewards and punishments (increased pain or pain relief) become greater. Deficits in 'neuroeconomic' decision-making that occur in association with the observed rCBF and GM alterations in key areas such as the DLPFC may reflect the less than optimal strategies employed by CLBP patients. GM increases in the basal ganglia reflect the demands of integrating and modulating sensory, cognitive and affective elements of the pain experience in order to plan and execute motor strategies. Deficits in motor strategies seen by clinicians managing low back pain have usually been attributed to local tissue pathology and spawned a specialist industry using elaborate muscle training regimes ("core stability") with little evidence of efficacy (Lederman 2010). One may speculate that rather than local pathology, local muscle dysfunction and problems in recruitment and coordination of muscle groups may stem instead from higher order processes. In addition, the fact that GM alterations in the basal ganglia and motor cortex were seen in MLBP (and not NuLBP) subjects compared to controls possibly suggests that increases are an adaptive response in MLBP patients who are actively involved in integration of sensory and motor stimuli to coordinate motor

activity. However, dysregulation in pain modulatory systems such as the OFC and DLPFC and cingulate in the NuLBP population might make an appropriate motor response too challenging. The NuLBP population instead may direct resources towards vigilance and prevention of pain by reducing activity and less towards planning motor strategies as the behavioural data demonstrates. Therefore, the type of neuroplastic change revealed in the basal ganglia and motor cortex in my work may be a key indicator (in some patients) of the transition from mechanical to neuropathic back pain.

Furthermore, we witnessed GM and rCBF alterations in the anterior insula, which according to Domasio's somatic marker hypothesis is involved in emotional responses based on underlying physiological markers that influence decision-making. Dysregulation in the anterior insula may predicate the CLBP patient to a heightened emotional response (i.e fear/anxiety) in response to alterations in muscle tone/guarding. In turn a heightened emotional response may result in altered muscle response. Over time, the resultant muscle and emotional responses may become conditioned and account for the difficulty faced by physiotherapists in rehabilitating patients with aberrant movement patterns and sub-optimal muscle function.

In addition to the challenges and uncertainties of moving the physical body, the imaging data suggests that alterations in perfusion in the EBA and increased GM in the somatosensory and motor cortex may reflect the demands of maintaining a coherent body schema when the back no longer moves as it once did. Alterations in body schema and sense of self-identity

are present in CLBP and may reflect neuroplasticity in motor, and representational networks.

6.3 CLBP patients show evidence of alterations to body schema.

In addition to the challenges and uncertainties of moving the physical body detailed above, our imaging data suggest that increased GM in the somatosensory and motor cortex may also reflect the demands of maintaining a coherent body schema in the face of alterations to movement patterns, activity, muscle function and proprioception that have all been associated with CLBP and discussed in this thesis. Neuroplasticity in motor and representational networks relating to the virtual representation of the body and body schema have been described in CLBP and discussed extensively in this thesis. The imaging data show alterations in rCBF in 'higher' association areas (the extrastriatal body area (EBA) and posterior superior parietal cortex) involved in processing and integrating multisensory information concerned with representation of the state of one's own body. The behavioural data show an increasing sensory, cognitive and affective load that increases in line with an increasing neuropathic component as measured by painDETECT. Additionally, the examination data show that patients with CLBP have poorer sensory discrimination in both two point discrimination and tactile thresholds and that NuLBP patients have poorer tactile threshold discrimination than MLBP patients. I suggest that together these alterations in sensory discrimination are associated with changes

observed in areas that represent body schema such as the extrastriatal body area, posterior parietal and somatosensory cortex. I speculate that the loss of discrimination may reflect a deeper loss of a sense of embodiment and connection to the physical being, the sense of being secure and stable in a physical identity that has been discussed in relation to the phenomenon of neglect experienced by patients with chronic pain and CLBP. I suggest that the neuroimaging data and subtle changes in discrimination thresholds relate to a diminution of the sense of ownership of the body and ultimately, self-identity. Our behavioural data demonstrate the profound impact of CLBP not only on physical but also mental health across a number of physical, emotional and psychological domains that suggest the struggle of the CLBP sufferer to maintain a representation of an established self-identity associated with a role in family, social and work settings. The multi-dimensional impact of CLBP undermines the old familiar self-identity and body schema that is associated with normal pain-free activity and function. In addition, I suggest that body image is linked not only to the physical dimensions of the experience of LBP but the poorer mental health scores that reflect an existential anxiety, loss of agency and uncertainty about the sufferer's place in a world that is limited by low back pain. Indeed, at some level, reductions in tactile sensitivity may represent an adaptive response by the sufferer to free themselves from the "enmeshment" postulated by Pincus and Morley (Pincus and Morley 2001) in which pain in the body becomes entangled with a rejected and negative view of the self, forming an "enmeshment" from which the patient cannot escape. This is likely to occur at the supraspinal level and may correlate to the structural and functional

plasticity observed in my study. These representational changes may be an adaptive strategy that the nervous employs to free the person from this enmeshment by reducing attentional resources.

I suggest therefore that this study's examination, imaging and behavioural data represent a loss of psychological and physical well-being in CLBP may even extend to the sense of self-identity and self-worth and ownership of agency. Although these ideas are speculative, it would be interesting to explore further the relationships between body schema, body image, examination data (proprioception, sensory discrimination) and qualitative analysis employing a combined cognitive psychology and neuroimaging approach.

6.4 Grey Matter and rCBF Group Differences (as identified by PainDETECT) Do Not Relate To Differences in Psychological Variables scores.

Our results showed that there was negligible overlap between areas in which regression analysis showed a significant relationship between GM and rCBF alterations and psychological variables (CES-D and STAI state) and ANOVA group comparison areas in which GM and rCBF differences were seen. These results strongly indicate that that GM and rCBF differences that were identified in the CLBP, MLBP and NuLBP groups were not related to these psychological variables.

6.5 **Neuroplasticity and neuropathic pain.**

CLBP patients in this study demonstrate a continuum of painDETECT scores that show a clinical spectrum from definitely non-neuropathic (i.e. mechanical), through 'unclear', to definitely having a significant neuropathic component. Whilst an explanation based on peripheral nervous system mechanisms may account for the location of the patient on the continuum, I suggest an alternative, that spinal and supraspinal mechanisms, especially in the absence of any lesion or disease mechanism, may also account for a neuropathic presentation. The neuroimaging data from this study shows clear signs of structural and functional neuroplasticity in patients with CLBP compared to controls and, of particular relevance to this discussion, NuLBP patients compared to MLBP. Unfortunately, functional and structural MRI are not sensitive enough media to demonstrate the exact underlying mechanisms at play. However, throughout this thesis I have presented evidence from studies of CLBP and other pain conditions that show that structural, functional and chemical neuroplasticity is associated with chronic pain. Animal models demonstrate evidence of sensitised neurones not only in the in the dorsal horn (Woolf and Salter 2000, Woolf 2011) but also in the brain (Guilbaud, Benoist et al. 1992, Paulson, Casey et al. 2002). Neuropathic pain profiles, outside classic textbook descriptions may occur due to spinal and supraspinal mechanisms, despite no obvious lesion state (Wall 1991).

I suggest that this calls in to question the validity of the IASP redefinition of neuropathic pain requiring a lesion or disease and rather suggests that the

pain experience, in itself, may lead to supraspinal neuroplastic changes as demonstrated by my data and a large body of literature. These neuroplastic changes may then constitute an ‘injury’ to the nervous system i.e. the pain experience itself ‘pathologises’, leading to the constellation of signs and symptoms that fulfil the diagnostic criteria of neuropathic pain.

I suggest that the painDETECT score continuum reflects an increasingly ‘pathologised’ nervous system resulting in an increasing predominance of neuropathic mechanisms. Patients at the lowest ‘mechanical’ end of the scale are thought to have symptoms that are mediated primarily by nociceptive input from tissue-based pathology - these are patients who should respond to tissue-based treatments, whether pharamacological or physically based. The behavioural data from this study supports the clinical observation that they are generally less in need of psychological support. Further along the continuum, increasing signs and symptoms across a broad range of domains, not just pain intensity, show a clinical picture that may be mediated by an increasingly dysfunctional or maladaptive CNS. The behavioural manifestations of increasing dysregulation of the CNS are shown in our behavioural data and in the wide range of clinical presentations across a broad range of domains reflecting the multi-dimensional nature of the chronic neuropathic pain experience.

The data from this study show that CLBP is not simply a sensory-discriminatory disorder but is associated with increasing psychological comorbidity and pain severity as the neuropathic component increases. This is consistent with studies showing the burden of neuropathic pain on quality

of life across a number of domains (Dworkin 2002, Jensen, Chodroff et al. 2007). This study's neuroimaging data have shown volumetric and rCBF changes in multiple regions implicated in both pain and mood that may account for the impact of CLBP and NuLBP across both sensory and psychological dimensions.

Mayberg has described chronic depression as a failure of homeostatic self-regulation in the face of overwhelming stressors (Mayberg 2009). Behavioural data from this study show that CLBP and in particular NuLBP patients have to deal with considerable pain and psychological stressors. I therefore suggest that the linear relationship between pain and psychological comorbidities demonstrated along the neuropathic continuum in our data reflect the failure of self-regulation across a number of domains associated with increasing neuropathic mechanisms. Neuroimmune interactions may underlie psychological and pain comorbidities (Walker, Kavelaars et al. 2014) which, in turn, may cause changes to brain structure and function (Borsook, Maleki et al. 2012, Vachon-Presseau, Roy et al. 2013). Investigation of this hypothesis would involve a new study paradigm in itself, which could provide a useful avenue for future work.

I suggest, therefore, that, it is time to abandon a dualistic approach to pain and pain comorbidities, and to stop treating them clinically and conceptually as separate entities. Rather, chronic pain needs to be reconsidered as a multidimensional experience, involving sensory-discriminative, affective-motivational and cognitive-evaluative components. Treatment that focuses on tissue-based mechanisms distracts from an understanding of pain along

the neuropathic continuum as a product of maladaptive neuropathic CNS mechanisms. I suggest that the grey matter and rCBF alterations in the neuroimaging data, the altered sensory profiles in the examination data and the behavioural data demonstrate the impact of chronic pain and are correlates of neuropathic mechanisms. Novel treatments need to be developed to target not only sensory and psychological components of chronic back pain but also to address the dysfunctional maladaptive supraspinal plasticity that this thesis has identified.

Initial efforts to develop therapies targeting supraspinal neuroplastic changes have begun and have their origin in the management of CRPS and phantom limb pain. In common with back pain and my data, these painful conditions are characterised by a profile of behavioural, sensory-motor and neuroplastic alterations.

The methods employed to manage these conditions have included both motor re-education and sensory discrimination re-education strategies (see (Moseley and Flor 2012) for an extensive review of the literature). At present there is a paucity of data available on their use in CLBP. It is likely that one future direction will be an attempt to directly alter brain activation by brain stimulation or neurofeedback either in isolation or as adjuncts to behavioural treatments. In addition, visualisation or virtual reality technologies might be used to re-establish cortical mapping and body schema. Another possible strategy may involve extinction training, either in isolation or combined with pharmacological interventions that directly modulate plasticity and enhance extinction of specific symptoms and/or behaviours.

6.6 Do the neuroimaging results show a neuropathic pain signature?

A key aim of this thesis was to establish if there is a cortical signature for CLBP and, in particular, neuropathic low back pain, in order to develop potential clinical biomarkers for CLBP. These biomarkers could be used to identify underlying mechanisms and differentiate mechanistic processes in CLBP. A recent study (Gustin, Peck et al. 2011) has attempted to similarly compare and contrast morphometric profiles of trigeminal neuropathic pain patients compared to tempromandibular (TMD) patients using VBM. Using their own data and findings of others, the authors asserted that neuropathic pain is strongly associated with thalamic atrophy (Gustin, Peck et al. 2011).

In contrast, my data has shown evidence of increased GM volume in the margin of the right thalamus in CLBP patients. Other VBM CLBP studies show similarly conflicting data; reductions (Apkarian, Sosa et al. 2004, Ivo, Nicklas et al. 2013), increases (Schmidt-Wilcke, Leinisch et al. 2006, Wu, Inman et al. 2013), and no significant alterations (Buckalew, Haut et al. 2008, Seminowicz, Wideman et al. 2011, Kong, Spaeth et al. 2013). It is difficult to therefore to draw any firm conclusions from these studies. Variation in results may be due to differences in patient selection criteria and methodologies employed. Together with my data this body of work challenges the legitimacy of the proposal by Gustin et al that thalamic atrophy is a reliable biomarker of neuropathic pain.

Functional alterations have also been reported, for example a reduction in thalamic blood flow has also been suggested as a biomarker for spontaneous neuropathic pain (Haanpaa, Attal et al. 2011). Historical PET studies of either neuropathic pain or pain suggestive of a significant neuropathic component, have mainly reported reductions in rCBF (Di Piero, Jones et al. 1991, Hsieh, Belfrage et al. 1995, Peyron, Garcia-Larrea et al. 1995, Garcia-Larrea, Peyron et al. 1999) although one study has showed thalamic hyperactivity (Cesaro, Mann et al. 1991). However, all of these studies used extremely small patient groups of between two and five subjects and all used methods to reduce pain in their subjects, in order to compare the painful state with a pain-free state, rather than comparing patients in pain with healthy controls. Evidence from structural and functional neuroimaging studies carried out since this early work and detailed throughout this thesis, shows that fundamental neuroplastic changes occur in patients with chronic pain, making them unsuitable for use as control subjects, even in the pain free state. Clearly, in light of these limitations, care must be exercised in interpreting these studies. A recent study, found thalamic and brainstem rCBF decreases in neuropathic PTN subjects (but not non-neuropathic TMD disorder subjects, using ASL (Youssef, Gustin et al. 2014). However, we did not demonstrate any alterations in thalamic rCBF in CLBP overall (in line with another recent ASL CLBP study (Wasan, Loggia et al. 2011) and furthermore, I found no alterations in the individual analysis of mechanical or neuropathic subgroups.

I suggest that data is lacking at present to support the idea of specific structural or functional regional neuroimaging ‘signatures’ associated with neuropathic pain, nor is there evidence for a specific cortical signature for neuropathic pain.

My data show that CLBP patients overall, and MLBP and NuLBP subgroups, show distinct differences in structural and functional neuroimaging, clinical examination and behavioural profiles compared to healthy controls. I suggest that my behavioural and examination data are associated with the neuroplastic changes seen in the functional and structural imaging chapters. However, I believe that we are not yet able to say that we have discovered ‘biomarkers’ of mechanical and neuropathic low back pain. I think the search for a mechanical or neuropathic low back pain neuroimaging profile is conceptually problematic. The idea of a specific pain imaging neuromatrix has often been discussed in imaging literature (Tracey and Mantyh 2007) as if it were possible to identify an anatomically distinct pattern to identify the experience of pain. However, recent work has called this notion into question, suggesting that the communality of results in acute pain neuroimaging is rather more to do with stimulus saliency than with the experience of pain (Iannetti and Mouraux 2010). In this thesis, I have also demonstrated alterations within the saliency network, which adds support to this idea.

I would suggest, therefore, that the neuroimaging results seen in this study reflect the individual experience of CLBP patients across the sensory-discriminative, affective-motivational and cognitive-evaluative dimensions of

pain that I have discussed throughout this thesis. Each individual has a unique experience of pain. Across the groups however, all the data in this study clearly reflect the differences in pain intensity, affect and cognitive burden seen in chronic low back pain patients compared to healthy controls and in particular of NuLBP compared to MLBP patients.

Chapter 7 CONCLUSION

This body of work has demonstrated the ability to characterise CLBP using a battery of behavioural, examination and functional and structural neuroimaging methodologies. I have established that these modalities have the ability to differentiate between CLBP patients and controls and importantly, between NuLBP and MLBP patients. This work demonstrates the impact of CLBP across sensory-discriminative, affective-motivational and cognitive-evaluative dimensions of the pain experience and shows the increased impact and burden on those who suffer with neuropathic compared to mechanical low back pain.

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Appendix 1

IASP definition of neuropathic pain

Note: Neuropathic pain is a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria. The term lesion is commonly used when diagnostic investigations (e.g. imaging, neurophysiology, biopsies, lab tests) reveal an abnormality or when there was obvious trauma. The term disease is commonly used when the underlying cause of the lesion is known (e.g. stroke, vasculitis, diabetes mellitus, genetic abnormality). Somatosensory refers to information about the body per se including visceral organs, rather than information about the external world (e.g., vision, hearing, or olfaction). The presence of symptoms or signs (e.g., touch-evoked pain) alone does not justify the use of the term neuropathic. Some disease entities, such as trigeminal neuralgia, are currently defined by their clinical presentation rather than by objective diagnostic testing. Other diagnoses such as postherpetic neuralgia are normally based upon the history. It is common when investigating neuropathic pain that diagnostic testing may yield inconclusive or even inconsistent data. In such instances, clinical judgment is required to reduce the totality of findings in a patient into one putative diagnosis or concise group of diagnoses.

Central neuropathic pain: Pain caused by a lesion or disease of the central somatosensory nervous system. See neuropathic pain note.

Peripheral neuropathic pain: Pain caused by a lesion or disease of the peripheral somatosensory nervous system. See neuropathic pain note.

Appendix 2

ASL Sequence

Arterial blood was labelled using a 1.5s train of Hanning radio frequency (RF) pulse of 500μs duration, with an inter-pulse period (τ) of 1500μs. The amplitude of each Hanning RF pulse was 8.4μT, (effective flip angle of 32.3 degrees). Gradient pulses of the same duration and repetition rate (each followed by a refocusing lobe) accompanied the RF train to achieve flow-driven adiabatic inversion.

We employed a post-labeling delay of 1.5 seconds. This delay has been found to be appropriate to minimize vascular artefacts (Alsop and Detre 1996, Dai, Garcia et al. 2008) and has been employed successfully in several studies that utilized a single TI ASL method in healthy volunteers (Howard, Krause et al. 2011, Howard, Sanders et al. 2012, Marquand, O'Daly et al. 2012, Towgood, Pitkanen et al. 2012, El-Hage, Zelaya et al. 2013, Handley, Zelaya et al. 2013). The image was acquired with a 3D Fast Spin Echo (FSE) spiral multi-slice readout. To minimize blurring, the spiral acquisition was very short (4ms), and the required resolution was achieved with 8 spiral interleaves (effective TE 32ms/TR = 5500ms; Echo Train Length (ETL) = 64). Images were acquired at a 48 x 64 x 60 matrix on a 18 x 24 x 18cm field of view and reconstructed to a 256^2 in plane matrix, resulting in a nominal spatial resolution of 1x1 x 3mm. For signal averaging purposes, three pairs of tagged-untagged images were collected in succession. Selective saturation of the image slab was applied at 4.3s before acquisition,

selective inversion was applied 3s before acquisition with further non-selective inversions at 1.5s, 764ms, 334ms and 84ms before imaging. This repeated inversion achieved successful suppression of the background static tissue signal, thus maximizing the sensitivity to blood perfusion (Maleki, Dai et al. 2012).

Following the three arterial spin labeling (ASL) control-label pair averages, reference images were acquired with the same imaging sequence but with inversion recovery preparation, instead of ASL. One sequence with saturation of 4.3s and then an inversion at 1650ms before imaging was used to create a fluid suppressed image. A second sequence with saturation at 4.3s and then inversion at both 2408ms and 511ms was also acquired to create a fluid and white matter suppressed image. For both these sequences, the receiver gain was automatically lowered by 21 dB relative to the ASL sequence to avoid receiver saturation. These images were used to quantify blood flow from the mean perfusion weighted difference image computed from the three tagged-untagged pairs, as described below. The sensitivity of the image was also calibrated to water at each voxel in order to account for the relative sensitivity of the coil elements (Williams, Detre et al. 1992, Alsop and Detre 1996, Buxton, Frank et al. 1998). By means of a neighborhood maximum algorithm to avoid regions with partial volume of suppressed fluid, a low-resolution sensitivity map was created. This map was calibrated for water sensitivity by assuming the tissue was predominantly white matter with a water concentration of 0.735 gm/ml (Herscovitch and Raichle 1985) and a T1 of 900ms, and using the equations for inversion

recovery signal attenuation. This calibration produced a sensitivity map, C, equal to the fully relaxed MRI signal intensity produced by one gm of water per ml of brain. It is worth noting that assuming pure grey matter produces only a 5% calibration difference. With this co-registered sensitivity map C, CBF was calculated at each voxel using the equation:

$$CBF = \frac{\rho_b \left(S_c - S_l\right)}{2\alpha C \omega_a T1_a \exp\left(-\frac{w}{T1_a}\right)\left(1 - \exp\left(-\frac{tl}{T1_a}\right)\right)}$$

where ρ_b is 1.05g/ml (the density of brain tissue; (Herscovitch and Raichle 1985)), α is the labeling efficiency (assumed to be 95% for labeling times 75% for background suppression; (Garcia, Duhamel et al. 2005), w is 1.5s (the post-labeling delay; (Alsop and Detre 1996)), tl is 500ms (the labeling duration), $T1_a$ is 1.4 ms (the T1 of arterial blood which was slightly lower than the value of (Lu, Clingman et al. 2004)), ω_a 0.85 g/ml (the density of water in blood(Herscovitch and Raichle 1985)), S_l and S_c are the signal intensities in the labeled and control images, respectively.

The whole ASL pulse sequence, including the acquisition of calibration images, was performed in 6:08min and repeated 4 times in succession during the scan. T1 and T2 weighted FSE images were acquired for co-registration and normalization and a fast spin echo fluid-attenuated inversion-

recovery (FLAIR FSE) scan was made in order to allow radiological assessment to exclude the presence of pathology.

Appendix 3

List of Medications and Previous Non-Conservative Treatment for CLBP subjects.

painDETECT Diagnostic Category	Diagnosis by treating Clinician	Gender	Age	Medication	Previous Non-Conservative Intervention
MLBP	MLBP	F	46	Paracetamol, co-codamol	
MLBP	MLBP	F	28	nil	Epidural, Facet Joint Injections
MLBP	MLBP	M	32	nil	
MLBP	MLBP	F	43	Ibuprofen	
MLBP	(L) S1 NR	F	21	Amitriptyline and paracetamol	
MLBP	Neurogenic claudication	M	41	nil	
MLBP	MLBP	M	48	nil	
MLBP	MLBP	M	26	nil	
MLBP	LBP	F	37	Co-codamol	
MLBP	MLBP	F	26	nil	
MLBP	LBP	F	34	nil	
MLBP	LBP	F	49	Paracetamol, naproxen	
MLBP	MLBP	F	33	nil	
MLBP	CLBP	F	46	Ibuprofen	
MLBP	MLBP	F	28	nil	
MLBP	MLBP	F	30	nil	
MLBP	Discogenic low back pain with lateral stenosis L4/5	M	50	Ibuprofen	
MLBP	MLBP	F	45	Co-codamol, paracetamol	
MLBP	MLBP	M	37	Co-dydramol	
MLBP	MLBP	F	54	nil	
MLBP	LBP	F	42	Pregablin, duloxetine	
MLBP	MLBP with L L5/S1 Sensory Radiculopathy	F	47	Co-codamol	
MLBP	NO INFO	M	50	Paracetamol, amitriptyline	Discectomy
MLBP	MLBP	F	28	Paracetamol, ibuprofen	
MLBP	MLBP	M	39	nil	
MLBP	MLBP	F	32	Paracetamol	
NuLBP	L4/L5 stenosis leading to L4/5 sciatica	M	31	Paracetamol	
NuLBP	NO INFO	M	50	Ibuprofen	
NuLBP	MLBP	M	35	Naproxen, Paracetamol,	
NuLBP	MLBP	M	25	nil	Nerve root injection
NuLBP	MLBP	F	40	Tramadol, cellebrex, imigram	
NuLBP	LBP	M	49	Amitriptyline	
NuLBP	MLBP	F	43	Dihydrocoedine, paracetamol	
NuLBP	MLBP & distribution leg pain	F	53	Tramadol	
NuLBP	MLBP	F	38	nil	
NuLBP	Lumbar canal STENOSIS	F	54	Paracetamol, Gabapentin	
NuLBP	MLBP +STENOSIS	M	47	Co-codamol, voltarol	Discectomy
NuLBP	Spinal canal stenosis L4/L5 with left L5 radiculopathy	F	51	Diclofenac, ibuprofen	
NuLBP	Spinal pain	F	46	Paracetamol, duloxatine, amitriptyline and pregabalin	
NuLBP	MLBP	F	31	nil	
NuLBP	MLBP	F	53	Co-dydramol,paracetamol	
NuLBP	Radicular pain L5 right leg	F	57	Clonazepam, co-codamol, diclofenac,	Nerve root, facet joint injections, radio frequency denervation
NuLBP	MLBP	F	52	Co-codamol, diclofenac	
NuLBP	L5 Nerve root pain	F	26	Coedine, diclofenac, diazepam	
NuLBP	LBP - left leg pain	F	49	Etoricoxib	
NuLBP	Left S1 nerve root	M	44	Ibuprofen	
NuLBP	LBP	F	26	Paracetamol, co-codamol, ibuprofen	
NuLBP	right L5 nerve root pain	M	48	Co-codamol, amitriptyline	
NuLBP	Mechanical LBP	F	29	Amitriptyline (long-term, finished 2 weeks previous to scan)	
NuLBP	L5 sens radiculopathy	M	48	Co-codamol, ibuprofen	epidural injections x 2